and outcome in intensive care patients with acute kidney injury treated with renal replacement therapy

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Thesis submitted to the Faculty of Medicine and Health Sciences in fulfillment of the requirements to obtain the degree of Doctor in Medicine and Health Sciences.

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A

ACS	Abdominal Compartment Syndrome
ADQI	Acute Dialysis Quality Initiative
AKI	Acute Kidney Injury
AKI-EPI	Acute Kidney Injury-Epidemiologic Prospective Investigation
AKI-RRT	Acute Kidney Injury treated with Renal Replacement Therapy
AKIKI	Artificial Kidney Initiation in Kidney Injury
AKIN	Acute Kidney Injury Network
ANZICS	Australian New Zealand Intensive Care Society Adult Patient Database
APACHE II score	Acute Physiology and Chronic Health Evaluation score
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Renal Failure
ATN	Acute Tubular Necrosis
ATN study	Acute renal failure Trial Network study
AUC ROC	Area Under the Curve of a Receiver Operating Characteristics Curve

B

BEST Kidney	Beginning and Ending Supportive Therapy for the Kidney
BP	Bodily Pain
BUN	Blood Urea Nitrogen

C

CA-AKI	Contrast Associated Acute Kidney Injury
CAVH	Continuous Arteriovenous Hemofiltration
CHD	Continuous Hemodialysis
CHEST	Crystalloid versus Hydroxyethyl Starch Trial
CI-AKI	Contrast Induced Acute Kidney Injury
CIN	Contrast Induced Nephropathy
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CRRT	Continuous Renal Replacement Therapy
CSICU	Cardiac Surgical Intensive Care Unit
CVVH	Continuous Venovenous Hemofiltration
CVVHD	Continuous Venovenous Hemodialysis
CVVHDF	Continuous Venovenous Hemodiafiltration

D

Da	Dalton
DD	Dialysis Dependency

E

EGDT	Early Goal Directed Therapy
(e)GFR	(estimated) Glomerular Filtration Rate
EPO	Erythropoietin
EQ-5D	European Quality of Life 5 Dimensions questionnaire

ESKD	End Stage Kidney Disease
ESRD	End Stage Renal Disease

F

FDA	Food and Drug Administration
FF	Filtration Fraction
FINNAKI	Finnish Acute Kidney Injury

G

GFR	Glomerular Filtration Rate
GH	General Health
GP	General Practitioner

H

HD	Hemodialysis
HES	Hydroxyethyl Starch
HF	Hemofiltration
HrQOL	Health related Quality of Life

I

ICD-9	International Classification of Diseases, 9th Revision
ICU	Intensive Care Unit
IHD	Intermittent Hemodialysis
IGFBP-7	IGF-Binding Protein-7
IL	Interleukin
IIT	Intensive Insulin Therapy
IV	Intravenous

K

KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney Injury Molecule-1

L

L-FABP	Liver-type Fatty Acid-Binding Protein
LDH	Lactate Dehydrogenase
LOS	Length Of Stay

M

MACE	Major Adverse Cardiac Events
MAKE	Major Adverse Kidney Events
MCS	Mental Component Score
MDRD	Modification of Diet in Renal Disease
MH	Mental Health
MICU	Medical Intensive Care Unit

N

NA	Not Available
NAC	N-Acetylcystein
NGAL	Neutrophil gelatinase-associated lipocalin
NHP	Nottingham Health Profile
NO	Nitrous Oxide
NSAID	Nonsteroidal Anti-inflammatory Drug

O

OR	Odds Ratio

P

PCS	Physical Component Score
PD	Peritoneal Dialysis
PDMS	Patient Data Management System
PF	Physical Functioning
PRO	Patient Reported Outcome

Q

QALY	Quality Adjusted Life Years
QOL	Quality Of Life

R

RCT	Randomized Controlled Trial
RE	Role Emotional
RENAL	Randomized Evaluation of Normal versus Augmented Level Replacement Therapy
RIFLE	Risk, Injury, Failure, Loss of Kidney Function, End Stage Renal Disease
RP	Role Physical
RR	Relative Risk
RRT	Renal Replacement Therapy

S

SAPS	Simplified Acute Physiology Score
sCr	serum Creatinine
SD	Standard Deviation
SF	Social Functioning
SICU	Surgical Intensive Care Unit
SLA	Severe Lactic Acidosis
SLEDD	Slow Extended Daily Dialysis
SOFA	Sepsis-related Organ Failure Assessment
SOAP	Sepsis Occurrence in Acutely ill Patients

T

TMP	Transmembrane Pressure
TIMP-2	Tissue Inhibitor of MetalloProteinase-2

U

U	Urine
UF	Ultrafiltration
UO	Urine Output

V

VT	Vitality

Outline of the thesis

The present work focuses on the epidemiology and outcome of acute kidney injury (AKI) in critically ill patients treated with renal replacement therapy (RRT). All presented studies describe the epidemiology and (long-term) outcome of critically ill patients with AKI treated with RRT (AKI-RRT). Special attention was paid to timing of initiation of RRT in critically ill patients suffering from AKI. As an epidemiological research project we reported different types of endpoints.

Chapter 1 gives an introduction in the field of AKI starting with a short overview of the history of intensive care medicine with special focus on the historical milestones of AKI. It describes the epidemiological aspects, clinical consequences and management of AKI. It further briefly addresses the principles of dialysis. Controversial issues regarding RRT in critically ill patients with AKI are highlighted. Finally an overview of the different outcome measures used in epidemiological research is given.

Chapter 2 formulates the objectives and describes the methodology of the thesis.

Chapter 3 shows the results of a retrospective study evaluating whether conventional serum urea cut-off values as described in the literature were associated with outcome at time of initiation of RRT for AKI. It explores the impact of timing of initiation of RRT in the light of patient outcome.

Chapter 4 presents the results of an observational cohort analysis describing the epidemiology of severe lactic acidosis in critically ill patients with AKI treated with RRT. In addition factors that may influence outcome in these patients were evaluated.

Chapter 5 presents the results of a prospective cohort analysis evaluating the long-term patient and kidney outcomes in critically ill patients with AKI-RRT. It further assesses possible modifying factors of outcome such as chronic kidney disease (CKD), timing of initiation of RRT and RRT modality.

Chapter 6 presents the results of an observational matched cohort study assessing the long-term outcomes and quality-of-life of critically ill AKI-RRT patients at baseline, and at 3 months, 1 year and 4 years after ICU discharge and comparing quality of life with a cohort of matched non-AKI-RRT patients.

Chapter 7 discusses the results of the above mentioned studies.

Chapter 8 addresses some limitations of the present work and formulates some future perspectives.

Chapter 9 briefly summarizes the thesis.

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1. Critically ill patients

Modern day intensive care medicine was born in the early 1950s. The polio epidemic forced the anesthesiologist Dr. Ibsen from Copenhagen to set up the first intensive care unit (ICU) to take care of patients with respiratory insufficiency [1]. Over the past decades, intensive care has kept pace with the medical and surgical advances. ICUs evolved from small and restricted units to larger and technically high-end areas [2]. Modern ICU structures can be classified in several different models. In open-model ICUs patients are cared for by multiple specialists with or without the expertise as an intensivist. In a closed-model ICU a team of dedicated intensivists take care of critically ill patients. External specialists may be consulted. Apart from the open and closed-model classification, intermediate models of ICU structure also exist [3]. Modern day ICUs accommodate a very heterogeneous group of severely ill patients. Patients may be admitted because of severe trauma or demanding surgery. In addition, problems can be very complex. For example in sepsis patients suffer from multi-organ dysfunction, rather than a single physiological impairment [4]. A major limitation in treatment is the fact that many therapeutic options in critical care are supportive rather than curative in nature. In the case of severe AKI, RRT only supports the electrolyte, acid-base and volume balance, thus it cannot restore all renal functions. Furthermore, if organ failure is sustained, complex interactions with other organ systems and changes in the inflammatory response of the host will lead to subsequent deterioration. So even after a successful initial resuscitation episode, this host iflammatory process may lead to progressive multi-organ failure and eventually death [5]. In addition, a growing population of aging people has led to a change in case mix in ICU admissions. Nowadays, elderly patients of 65 years and older account for 42-52% of ICU admissions and for almost 60% of all ICU days [6]. Along with this geriatric population, the concept of frailty entered the ICU. Frailty is defined as a syndrome of loss of physical and psychological reserves that gives rise to increased vulnerability [7, 8]. Frail patients, with their higher prevalence of comorbidities and age-related loss of physical and cognitive reserves, form a new challenge for modern ICU care. Not surprisingly, actual determinants for long-term mortality in ICU patients are age, reason for ICU admission and preexisting comorbidities [9]. Until very recently, a historic emphasis on ICU mortality diverted attention from the post-ICU experience with its risk of long-term physical and psychological dysfunctioning and ongoing health care utilization threatened by increased rationing of limited health resources [10].

2. Critically ill patients with acute kidney injury

2.1. FROM “ISCHURIA RENALIS” TO “ACUTE KIDNEY INJURY”

In 1802 suppression of urine flow, depicted by Heberden as “ischuria renalis”, was recognized as a fundamental manifestation of renal disease. In the nineteenth century this disease was described in more detail and was named “Bright’s disease” after dr. Bright who studied patients presenting with decreased diuresis, followed by coma and

finally death [11, 12]. During World War I, "war nephritis" referred to renal granular and hyaline casts seen on histological specimens from critically ill soldiers suffering from a new renal disease characterized by symptoms of dyspnea and decreased urine flow [13]. During World War II, Bywaters and Beall were the first to describe in detail deterioration of renal function due to crush injury and rhabdomyolysis. Based on the histological findings in these kidneys the condition was called "acute tubular necrosis" (ATN) [14]. In 1946 the concept of "acute renal failure" (ARF) was introduced in literature by Frank. In 1951 Homer W. Smith described the concept of ARF in his textbook "The kidney – Structure and Function in Health and Disease". That same year a whole issue of the Journal of Clinical Investigation was dedicated to ARF [15]. ARF is defined as *"the abrupt loss of kidney function, resulting in the retention of urea and other waste products and in the dysregulation of extracellular volume and electrolytes"* [16]. Over the last decades this clinical picture has shifted from a single-organ disease to acute renal failure as part of multi-organ systemic illness predominantly occurring in ICU patients. In parallel more than 35 different definitions on ARF emerged in literature resulting in a wide variation in reported incidence from 1% to 25% in critically ill patients and mortality rates from 15 to 60% [17]. As a consequence comparative research on epidemiology and outcome of AKI was hampered and highlighted the need for a uniform definition of ARF.
The Acute Dialysis Quality Initiative (ADQI), a group of experts in the field of nephrology and intensive care, advocated this need in 2004 and proposed a new definition [18]. This resulted in the RIFLE classification, an acronym for Risk, Injury, Failure, Loss and End stage renal failure (RIFLE). This condition covers a spectrum of injuries this condition covers a spectrum of injuries comprising the whole range from mild impairment of renal function to the need of RRT. Definitions are based on changes in serum creatinine or urine output. The

Table 1.

Comparison between RIFLE, AKIN and KDIGO criteria.

	SCR AND GFR CRITERIA	URINE OUTPUT CRITERIA
RIFLE category		
Risk	sCr x1.5-1.9 OR 25% decrease in GFR from baseline	<0.5 ml/kg/h for ≥6 hours
Injury	sCr x2-2.9 OR 50% decrease in GFR rom baseline	<0.5 ml/kg/h for ≥12 hours
Failure	sCr x3 OR 75% decrease in GFR from baseline OR sCr>4mg/dl with an acute increase of at least 0.5 mg/dl	<0.3ml/kg/h for ≥24 hours OR anuria for ≥12 hours
Loss	Complete loss of renal function (RRT) for > 4 weeks	
End stage kidney disease	RRT > 3 months	
AKIN criteria		
Risk	sCr increase ≥ 0.3 mg/dl increase OR sCR x1.5-2-fold from baseline	<0.5ml/kg/h for ≥6 hours
Injury	sCr increase > 2-3-fold from baseline	<0.5ml/kg/h ≥12 hours
Failure	sCr increase > 3-fold from baseline OR sCr ≥4 mg/dL with an acute increase of at least 0.5 mg/dl or RRT	<0.3ml/kg/h for ≥24 hours OR anuria for ≥12 hours
KDIGO criteria		
Stage 1	sCr increase ≥ 0.3 mg/dl increase OR sCR x1.5-1.9-times from baseline	<0.5ml/kg/h for 6-12 hours
Stage 2	sCr increase > 2-2.9-times from baseline	<0.5ml/kg/h ≥12 hours
Stage 3	sCr increase > 3.0-fold from baseline OR sCr ≥4 mg/dL OR RRT OR eGFR<35mL/min/1.73m^2 in patients < 18 years	<0.3 ml/kg/h for ≥24 hours OR anuria for ≥12 hours

RIFLE classification was later modified by the Acute Kidney Injury Network (AKIN) group, stressing the importance of small declines in kidney function [19]. This group also introduced the present day term "Acute Kidney Injury". Later, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI harmonized the previous definitions and staging systems proposed by ADQI and AKIN [20]. The differences between the AKI staging systems are presented in **Table 1.**

2.2. Incidence of AKI in critically ill patients To obtain an overall concept on the incidence of AKI in critically ill patients, two landmark studies can be put forward. In 2005 Uchino and colleagues presented the Beginning and Ending Supportive Therapy (BEST) for the Kidney study, a multinational, multicenter, prospective epidemiological study of ARF on 29,269 patients [16]. They found an incidence of ARF in the ICU of approximately 6%. ARF was defined as a urine output of < 200 mL in 12 hours and/or a blood urea nitrogen (BUN) level > 84 mg/dL (> 30 mmol/L). More recently Hoste and colleagues demonstrated in The Acute Injury-Epidemiologic Prospective Investigation (AKI-EPI) study an incidence of AKI in 1,032 out of 1,802 ICU patients (57.3%) [21]. AKI was diagnosed and classified on the basis of the worst serum creatinine or urine output criteria according to the KDIGO classification. This wide variation in the rates of AKI in critically ill patients can be explained in several ways. First, the applied definitions of AKI in the above mentioned studies were not uniform. Based on the applied definition, the BEST Kidney trial mainly focused on patients with severe AKI [16]. On the contrary, the KDIGO classification based definition of AKI used in the AKI-EPI trial encompasses less severe forms of AKI [21]. Nevertheless, AKI can be considered a common complication in critically ill patients. Secondly, aside from the definition used, an increase of AKI has been reported over time. This observation may be related to an increasing awareness of AKI but also because of the above mentioned change in case-mix of patients as geriatric patients with notable comorbidities [6, 22].

2.3. Causes and risk factors of AKI in critically ill patients AKI is a syndrome that encompasses the entire spectrum ranging from purely functional to completely structural dysfunction with the requirement of RRT. Classically, AKI is categorized into three types of etiology: prerenal, renal or intrinsic and post-renal AKI. Prerenal and postrenal failures describe conditions "outside" the kidney and are otherwise called "functional" renal failure. Intrinsic renal failure is due to conditions "inside" the kidney, so-called "structural" renal failure or ATN [23]. To date this somewhat artificial classification is still widely used in the clinical identification and treatment of AKI. For example, patients suffering from intrinsic renal pathologies such as acute glomerulonephritis, vasculitis or interstitial nephritis need an immediate diagnosis and a decidedly different treatment than that of patients with prerenal or postrenal AKI. Despite its widely use, this classification is being questioned as it is not supported by hard data. Assigning the diagnosis of prerenal or intrinsic AKI is difficult as the underlying pathophysiological mechanisms are not fully understood. There is also an unclear differentiation and nebulous overlap between functional and structural AKI. So prerenal and intrinsic AKI may co-exist in the same patient [24]. The rise in concentration of novel urinary biomarkers in patients with "solely prerenal AKI" suggests that cellular damage is already present in this prerenal phase of AKI [25]. Novel biomarkers such as urinary NGAL may shed a new light on the discussion but their diagnostic discriminatory value should not be overemphasized [26].
Risk factors for AKI can be classified into baseline or preadmission risks, acute clinical conditions and agents associated with the development of AKI [27]. Older age, diabetes and heart failure typically predispose to AKI. However, the most important risk factor for AKI is preexisting CKD. Patients with underlying CKD have a ten-fold increased risk of the development of AKI. The underlying mechanisms of this acute-on-chronic kidney failure include impairment of autoregulation, abnormal vasodilatation and side effects of medication (antihypertensive agents, diuretic agents).

Further, a number of acute clinical conditions have been identified as risk factors for AKI. Sepsis accounts for most cases of AKI (21.0 to 47.5%) in critically ill patients [16, 21]. The etiology of AKI in critically ill patients with sepsis is usually multifactorial and frequently develops from a combination of hypovolemia, nephrotoxic effects by medications and hemodynamic perturbations [28]. Other frequent clinical conditions that may increase the risk of AKI in critically ill patients are major surgery and trauma, intra-abdominal hypertension and intra-abdominal compartment syndrome, cardiogenic shock, hypovolemia and hepatorenal syndrome. Finally, nephrotoxic agents such as NSAIDs or contrast media are associated with the development of AKI in critically ill patients [16, 29].

2.4. Novel biomarkers of AKI Currently, the standard diagnostic tools for AKI detection are sCr concentration and urine output. Both are markers of renal function but not kidney injury [30]. In the recent past, several potential biomarkers for AKI have been introduced. Ideally these novel biomarkers have the ability to identify the injury to the tubular system and to facilitate the diagnosis and the differential diagnosis of AKI. As a consequence they may identify patients who are going to develop AKI. Furthermore they could assist in the evaluation of the intensity of injury. Finally they should be prognostic relevant by predicting the need for RRT, AKI-related complications and short- and long-term prognosis [31]. This section describes the basic pathophysiology and the ability to predict outcome of the most important currently proposed biomarkers of AKI. The novel biomarkers can be classified into three groups. The first group encompasses inflammatory biomarkers including Neutrophil Gelatinase-Associated Lipocalin (NGAL) and pro-inflammatory cytokines such as IL-18. The second group includes cell injury biomarkers such as Kidney Injury Molecule 1 (KIM-1) and Liver-type Fatty Acid-Binding Protein (L-LFABP). The third recently identified group consists of cell cycle markers such as Tissue Inhibitor of MetalloProteinase-2 (TIMP-2) and IGF-Binding Protein-7 (IGFBP-7) [32, 33].

Inflammatory biomarkers NGAL is a 25-kDA protein of the lipocalin family. The known functions of NGAL are related to its ability to bind iron-siderophore complexes. It binds to free iron and exerts a bacteriostatic function by preventing iron uptake by bacteria [32]. NGAL is expressed at very low constant levels in different cell types. After ischemic, septic or toxic AKI it is highly upregulated in the thick ascending limb and the intercalated cells of the collecting duct [33]. NGAL is filtered by the glomerulus and is reabsorbed by the proximal tubules [34]. A decrease in tubular reabsorption after AKI may lead to a further increase in urinary NGAL concentration. Elevated NGAL protein is detectable in the urine as early as three hours after injury and peaks approximately 6 hours after injury. In severe injury the elevation can persist up to 5 days after the initial harmful event [35,36]. NGAL expression in AKI follows a dose-dependent curve with respect to the severity of kidney injury. Urine and plasma NGAL concentrations rise rapidly and proportionally to the severity and duration of the insult [25]. It is the most widely investigated new biomarker for AKI. The performance of NGAL was determined in different settings and populations. A recent meta-analysis including almost 3,000 cardiac surgery patients evaluated the performance of urinary NGAL and reported an AUC of 0.72 [37]. Interestingly, NGAL levels increase in the setting of stimuli damaging the kidney but not in the setting of rapidly reversible and fluid-sensitive volume depletion [38,39]. As such NGAL is able to separate volume depletion and intrinsic damage, two clinical separate entities making up the differential diagnosis in AKI. Further, in sepsis NGAL can rise days before sCr increases [33]. NGAL predicted death or RRT at the time of admission to the emergency room. Patients with NGAL > 104 ng/mL and sCr>1.4mg/dL demonstrated a 15% incidence of death or RRT during hospitalization [40]. Further Singer et al demonstrated an association between elevated urinary NGAL levels at AKI diagnosis and long-term adverse outcomes of ESRD or death [41]. IL-18, also known as interferon-gamma inducing factor is a 22-kDa proinflammatory cytokine [42]. It is synthesized by multiple

tissues, including monocytes, macrophages and the intercalated cells of the collecting ducts in healthy kidney [43]. Ischemia-reperfusion injury leads to an increase in IL 18 levels [44]. IL-18 is an attractive target for biomarker-directed therapy of AKI, because this cytokine seems to play a prominent role in the inflammatory processes that exacerbate renal injury during the extension phase of AKI. Urinary IL-18 is elevated within the first 6 h after renal injury and peaks after 12-18 hours. Only few clinical studies have analyzed the utility of IL-18 as a biomarker for AKI [45]. Although promising for the prediction of delayed graft function urinary IL-18 failed to show reliable prediction in the general ICU population [46].

Cell injury biomarkers KIM-1 is a 38-kDa transmembrane protein. Basal expression of KIM-1 is low in the normal kidney but is rapidly upregulated after ischemia-reperfusion injury. KIM-1 protein can be localized to proliferating dedifferentiated epithelial cells of the proximal tubule 48 hours after injury [47]. The late timing of peak changes (2-3 days after AKI) in urine KIM-1 concentrations suggests a functional role in the molecular and cellular biology of AKI associated with renal recovery and tubular regeneration after AKI. Unfortunately, studies evaluating the prognostic use of KIM-1A are rather disappointing [48]. Because increased KIM-1 can indicate either injury or repair, the concentration of KIM-1 by itself may not be able to discriminate between worsening AKI and injury which will recovery. Kim-1 has been approved by the US Food and Drug Administration as an AKI biomarker for preclinical drug development [49].

L-FABP is a 14k-Da protein expressed predominantly in the proximal tubule. L-FABP concentration elevates immediately after AKI and peaks within 6 hours [50]. It is a renoprotectif protein and has antioxidant properties by mitigating H2O2-induced oxidative stress. The L-FABP gene expression is induced by hypoxia and reduces the severity of renal ischemia-reperfusion injury [51]. L-FABP has already been approved as a diagnostic test for use in Japan. A study in ICU patients found that urinary L-FABP at the time of ICU admission predicted the development of AKI within 1 week (AUC=0.7), suggesting that patients with elevated baseline L-FABP values are at greater risk for the development of AKI [52]. Therefore L-FABP measurement may be used to identify high-risk patients and minimize their exposure to renal insults. In summary, urinary L-FABP appears to be a promising biomarker for both diagnosis and prediction of AKI and its outcomes among critically ill patients [53].

Cell cycle markers Each phase of the cell cycle has a specific function that is required for appropriate cell proliferation. Cells can use the cell cycle arrest as a protective mechanism to avoid cell division during stress and injury. Failure to achieve G1 cell cycle arrest can lead to an increased proportion of renal tubular cells in the G2/M phase, producing profibrotic growth factors that are capable of stimulating fibroblast proliferation and collagen production leading to kidney damage [54]. The cell cycle biomarkers TIMP-2 and IGFBP-7 are expressed in the tubular cells and involved in several biological processes, including cell cycle arrest [55]. Additionally, TIMP-2, a 21-kDa protein, is involved in the pathophysiology of ischemia-reperfusion injury. It promotes disease progression through the activation of metalloproteinase and triggering of tubulointerstitial fibrosis and injury. IGFBP-7 is a 29-kDa secreted protein that is a member of the IGFBP-related proteins. They exhibit pleiotropic effects in development and disease, and IGFBP-7 regulates the bioavailability of IGFs through direct low-affinity bindings [56]. By detecting cell cycle arrest markers in the urine, one may actually be detecting cell stress before injury has occurred. The Sapphire study tested the ability of 340 proteins involved in biological pathways presumably linked to the pathogenesis of AKI, to predict development of AKI in ICU patients [57]. The product of [TIMP-2] [IGFBP-7] provided an AUC of 0.80 (95% CI 0.74-0.84) for severe AKI in the validation cohort. Urinary [TIMP-2] [IGFBP-7] was significantly superior to all previously described markers of AKI ($p<0.002$), including NGAL and KIM-1 in forecasting AKI stage 2 or 3. The Topaz study validated [TIMP-2] [IGFBP-7]

in a multicenter study using clinical adjudication to determine the primary endpoint of moderate-severe AKI [58]. ICU patients with urinary [TIMP-2] [IGFBP-7] levels > 0.3 ng/ml2/1000 had 7 times the risk for AKI compared with ICU patients with a negative test result. On the contrary, a recent study from Bell et al found that in ICU patients the biomarker panel did not predict AKI within 24-48 hours [59]. In long-term follow-up of the original validation study (i.e. Sapphire study) Koyner et al explored the association of the combined biomarker and long-term outcome (9 months). A composite endpoint of mortality or the need for RRT was evaluated. Univariate analysis showed that [TIMP-2] [IGFBP-7] value of 2.0 was associated with increased risk of the composite endpoint (HR 2.11 (95% CI 1.37-3.23), P<0.001). In a multivariate analysis levels >0.3 were associated with death or RRT only in subjects who developed AKI. They concluded that the combined biomarker measured early in the setting of critical illness may identify patients with AKI at increased risk for mortality or receipt of RRT over the next 9 months [60]. At present 3 kidney damage biomarkers are available for clinical use: neutrophil gelatinase-associated lipocalin (NGAL), and the combination of insulin-like growth factor-binding protein IGFBP-7 and TIMP-2 or urinary [TIMP-2] [IGFBP-7]. Unfortunately there is no perfect biomarker of AKI. Each of the described biomarkers is not entirely specific for AKI and demonstrates imperfect test characteristics. However, the novel biomarkers will likely develop a deeper understanding of kidney injury, giving clinicians more powerful tools in the decision-making.

2.5. Evolution from AKI to CKD: pathophysiological insights AKI, regardless of its etiology, is associated with a greater risk of CKD and with progression to ESRD. The pathophysiological mechanisms of renal injury and repair include vascular, tubular and inflammatory factors [61].

Vascular factors The kidney has a high oxygen demand with a relatively low O2 extraction. In addition, the oxygenation of the outer medulla is quite marginal making this region very susceptible to reduced vascular perfusion and oxygenation [62,63]. Injury to the microvascular endothelium leads to oxidative stress and the expression of cell surface markers that promote recruitment and adhesion of leukocytes and platelets. Subsequently, increasing vascular permeability induces interstitial edema and further reduces blood flow and oxygen delivery. These processes result in additional cell injury and inflammation [64]. The long-term consequence is a reduction in the number of microvessels in the kidney, potentially facilitated by the down-regulation of VEGF (vascular endothelial growth factor) and TGF-beta (transforming growth factor beta) and upregulation of angiogenesis inhibitors [65].This so-called “vascular dropout” may trigger a positive feedback process by which the loss of vessels results in hypoxia to areas of the nephron which than generate hypoxia-inducible factors. This chronic hypoxia may induce proinflammatory responses and cellular infiltrate leading to increased tubulointerstitial fibrosis and nephron loss [66].

Tubular factors AKI leads to an alteration of tissue architecture and cell structure. Injury induces a disruption of normal cell-cell interactions, a rapid loss of proximal tubular cell and cytoskeletal integrity and cell polarity. There is shedding of the proximal tubule brush border into the lumen and a desquamation of viable and nonviable cells leaving regions where the basement membrane remains the only barrier between the filtrate and the peritubular interstitium [67,68]. Severe injury may result into apoptosis and necrosis of tubular cells, but also impairs the epitelial proliferative response with cell cycle arrest at the G2/M phase of the cell. This process activates a signaling cascade that acts to upregulate profibrotic cytokines production [69].

Inflammatory factors AKI is an inflammatory disease characterized by the recruitment of various immune cells such as macrophages and T cells to the injured kidney tissue [70].Together with dendritic cells, this cellular infiltrate contributes to both parenchymal damage and fibrosis

by releasing inflammatory mediators. On the contrary, the cellular infiltrate also directly activates naive T cells providing a protective response and beneficial effects on repair [71,72].Further, the recruitment of monocytes may determine the ultimate fate of the tissue after injury: complete repair with little sequelae versus fibrosis with a tendency to progress to CKD. Although renal recovery from injury is possible through regeneration by surviving tubular epithelial cells, AKI may result in incomplete repair with persistent tubulointerstitial inflammation and the transformation of epithelial cells into fibroblasts contributing to fibrosis [73,74]. The vascular dropout and tubulointerstitial fibrosis are hallmarks of CKD. Especially in the setting of underlying kidney disease, this maladaptive repair may enhance the worsening of CKD and the progression to ESKD [75].

REFERENCES

[1] Kelly FE, Fong K, Hirsch N, Nolan JP: Intensive care medicine is 60 years old: the history and future of the intensive care unit. Clin Med (Lond) 2014, 14(4):376-379.

[2] Vincent JL, Creteur J: Paradigm shifts in critical care medicine: the progress we have made. Crit Care 2015, 19 Suppl 3:S10.

[3] Garland A, Gershengorn HB: Staffing in ICUs: physicians and alternative staffing models. Chest 2013, 143(1):214-221.

[4] Martin GS: Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther 2012, 10(6):701-706.

[5] Rossaint J, Zarbock A: Pathogenesis of Multiple Organ Failure in Sepsis. Crit Rev Immunol 2015, 35(4):277-291.

[6] Marik PE: Management of the critically ill geriatric patient. Crit Care Med 2006, 34(9 Suppl):S176-182.

[7] McDermid RC, Stelfox HT, Bagshaw SM: Frailty in the critically ill: a novel concept. Crit Care 2011, 15(1):301.

[8] Rockwood K: What would make a definition of frailty successful? Age Ageing 2005, 34(5):432-434.

[9] Brinkman S, Bakhshi-Raiez F, Abu-Hanna A, de Jonge E, de Keizer NF: Determinants of mortality after hospital discharge in ICU patients: literature review and Dutch cohort study. Crit Care Med 2013, 41(5):1237-1251.

[10] Vandijck DM, Oeyen S, Decruyenaere JM, Annemans L, Hoste EA: Acute kidney injury, length of stay, and costs in patients hospitalized in the intensive care unit. Acta Clin Belg 2007, 62 Suppl 2:341-345.

[11] Fife G: Dr. Fife's Case of Ischuria Renalis. Prov Med Surg J (1840) 1840, 1(13):211-212.

[12] Eknoyan G: Emergence of the concept of acute kidney injury.

Adv Chronic Kidney Dis 2008, 15(3):308-313.

[13] Lameire N: Wars, disasters and kidneys. Acta Clin Belg 2014, 69(6):418-425.

[14] Bywaters EG, Beall D: Crush Injuries with Impairment of Renal Function. Br Med J 1941, 1(4185):427-432.

[15] Oliver J, Macdowell M, Tracy A: The pathogenesis of acute renal failure associated with traumatic and toxic injury; renal ischemia, nephrotoxic damage and the ischemic episode. J Clin Invest 1951, 30(12:1):1307-1439.

[16] Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E et al: Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005, 294(7):813-818.

[17] Kellum JA, Levin N, Bouman C, Lameire N: Developing a consensus classification system for acute renal failure. Curr Opin Crit Care 2002, 8(6):509-514.

[18] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, workgroup ADQI: Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004, 8(4):R204-212.

[19] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Network AKI: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007, 11(2):R31.

[20] Group KDIGO AKI Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. In., vol. 2. Kidney inter., Suppl.; 2012: 1-138.

[21] Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D et al: Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015, 41(8):1411-1423.

[22] Rewa O, Bagshaw SM: Acute kidney injury-epidemiology, outcomes and economics. Nat Rev Nephrol 2014, 10(4):193-207.

[23] Lameire N, Van Massenhove J, Van Biesen W: What is the difference between prerenal and renal acute kidney injury? Acta Clin Belg 2012, 67(5):309-314.

[24] Belcher JM, Parikh CR: Is it time to evolve past the prerenal azotemia versus acute tubular necrosis classification? Clin J Am Soc Nephrol 2011, 6(10):2332-2334.

[25] Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M et al: The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 2011, 57(17):1752-1761.

[26] Van Biesen W, Van Massenhove J, Lameire N, Vanholder R: Does urinary neutrophil gelatinase-associated lipocalin really solve the issue of discriminating prerenal from intrinsic acute kidney injury? Kidney Int 2012, 81(3):321; author reply 321-322.

[27] Leblanc M, Kellum JA, Gibney RT, Lieberthal W, Tumlin J, Mehta R: Risk factors for acute renal failure: inherent and modifiable risks. Curr Opin Crit Care 2005, 11(6):533-536.

[28] Mårtensson J, Bellomo R: Sepsis-Induced Acute Kidney Injury. Crit Care Clin 2015, 31(4):649-660.

[29] De Waele JJ, De Laet I, Malbrain ML: Understanding abdominal compartment syndrome. Intensive Care Med 2016, 42(6):1068-1070.

[30] Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. Clin Chem Lab Med. 2017

[31] Szerlip HM, Chawla LS. Predicting acute kidney injury prognosis. Curr Opin Nephrol Hypertens. 2016;25(3):226-31

[32] Goetz DH, Holmes MA, Borregaard N, Bluhm ME, Raymond KN, Strong RK. The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. Mol Cell 2002;10:1033-1043

[33] Parravicini E, Nemerofsky SL, Michelson KA, Huynh TK, Sise ME, Bateman DA, Lorenz JM, Barasch JM. Urinary neutrophil gelatinase-associated lipocalin is a promising biomarker for late onset culture-positive sepsis in very low birth weight infants. Pediatr Res 2010;67:636-640

[34] Hvidberg V, Jacobsen C, Strong RK, Cowland JB, Moestrup SK, Borregaard N. The endocytic receptor megalin binds the iron transporting neutrophil-gelatinase-associated lipocalin with high affinity and mediates its cellular uptake. FEBS Lett. 2005 Jan 31;579(3):773-7

[35] Mishra, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil-gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365:1231-1238

[36] Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 2011;22:1748-1757

[37] Ho J, Tangri N, Komenda P, Kaushal A, Sood M, Brar R, Gill K, Walker S, MacDonald K, Hiebert BM, Arora RC, Rigatto C. Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: a meta-analysis. Am J Kidney Dis 2015;66:993-1005

[38] Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barash N, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann intern Med 2008;148:810-819

[39] Singer E, Elger A, Elitok S, Kettritz R, Nickolas TL, Barasch J, et al. Urinary neutrophil gelatinase-associated lipocalin distinguishes prerenal from intrinsic renal failure and predicts outcomes. Kidney Int 2011;80:405-414

[40] Nickolas TL, Schmidt-Ott KM, Canetta P, Forster C, Singer E, Sise M, Elger A, et al. Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective cohort study? J Am Coll Cardiol 2012, 59:246-55

[41] Singer E, Schrezenmeier EV, Elger A, et al. Urinary NGAL-positive acute kidney injury and poor long-term outcomes in hospitalized patients. Kidney International reports. In press.

[42] Novick D, Kim S, Kaplanski G, Dinarello CA. Interleukin-18, more than a Th1 cytokine. Semin Immunol. 2013 Dec 15;25(6):439-48

[43] Gauer S, Sichler O, Obermüller N, Holzmann Y, Kiss E, Sobkowiak E, Pfeilschifter J, Geiger H, Mühl H, Hauser IA. IL-18 is expressed in the intercalated cell of human kidney. Kidney Int. 2007 Nov;72(9):1081-7

[44] Franke EI, Vanderbrink BA, Hile KL, Zhang H, Cain A, Matsui F, Meldrum KK. IL-18 is macrophage independent during obstructive injury. PLoS One. 2012;7(10):e47417

[45] Lin X, Yuan J, Zhao Y, Zha Y. Urine interleukin-18 in prediction of acute kidney injury: a systematic review and meta-analysis. J Nephrol 2015;28:7-16

[46] Nisula S, Yang R, Poukkanen M, Vaara ST,

Kaukonen KM, Tallgren M, et al. Predictive value of urine interleukin-18 in the evolution and outcome of acute kidney injury in critically ill adult patients. Br J ANaesth 2015, 114:460-8

[47] Ichimura T, Bonventre JV, Bailly V, Wei H, Hession CA, Cate RL, Sanicola M. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem. 1998 Feb 13;273(7):4135-42.

[48] Hall IE, Coca SG, Perazella MA, Eko UU, Luciano RL, Peter PR, Han WK, Parikh CR. Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. Clin J Am Soc Nephrol. 2011 Dec;6(12):2740-9

[49] Dieterle F, Sistare F, Goodsaid F, Papaluca M, Ozer JS, Webb CP, et al. Renal biomarker qualification submission: a dialog between the FDA-EMEA and Predictive Safety Testing Consortium. Nat Biotechnol. 2010 May;28(5):455-62

[50] Maatman RG, Van Kuppevelt TH, Veerkamp JH. Two types of fatty acid-binding protein in human kidney. Isolation, characterization and localization. Biochem J. 1991 Feb 1;273 (Pt 3):759-66

[51] Yamamoto T, Noiri E, Ono Y, Doi K, Negishi K, Kamijo A, Kimura K, Fujita T, Kinukawa T, Taniguchi H, et al. Renal L-type fatty acid--binding protein in acute ischemic injury. J Am Soc Nephrol. 2007 Nov;18(11):2894-902

[52] Doi K, Negishi K, Ishizu T, Katagiri D, Fujita T, Matsubara T, Yahagi N, Sugaya T, Noiri E. Evaluation of new acute kidney injury biomarkers in a mixed intensive care unit. Crit Care Med. 2011 Nov;39(11):2464-9

[53] Cho E, Yang HN, Jo SK, Cho WY, Kim HK. The role of urinary liver-type fatty acid-binding protein in critically ill patients. J Korean Med Sci. 2013 Jan;28(1):100-5

[54] Yang L, Besschetnova TY, Brooks CR, Shah JV, Bonventre JV. Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. Nat Med. 2010 May;16(5):535-43

[55] Vijayan A, Faubel S, Askenazi DJ, Cerda J, Fissell WH, Heung M, Humphreys BD, Koyner JL Clinical Use of the Urine Biomarker [TIMP-2] × [IGFBP7] for Acute Kidney Injury Risk Assessment. Am J Kidney Dis. 2016 Jul;68(1):19-28

[56] Hwa V, Oh Y, Rosenfeld RG. The insulin-like growth factor-binding protein (IGFBP) superfamily. Endocr Rev. 1999 Dec;20(6):761-87

[57] Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013, 17:1.

[58] Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, Fitzgerald R, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med. 2014 Apr 15;189(8):932-9

[59] Bell M, Larsson A, Venge P, Bellomo R, Mårtensson. Assessment of cell-cycle arrest biomarkers to predict early and delayed acute kidney injury.J. Dis Markers. 2015;2015:158658

[60] Koyner JL, Shaw AD, Chawla LS, et al. Tissue Inhibitor Metalloproteinase-2 (TIMP-2) IGF-Binding Protein-7 (IGFBP7) Levels Are Associated with Adverse Long-Term Outcomes in Patients with AKI. J Am Soc Nephrol JASN 2015, 26:1747–1754

[61] Yang L, Humphreys BD, Bonventre JV. Pathophysiology of acute kidney injury to chronic kidney disease: maladaptive repair. Contrib Nephrol Basel, Karger,2011;147:149-155

[62] Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Investig. 2011;121:4210-21

[63] Ferenbach DA, Bonventre JV. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol 2015;11:264-76

[64] Zuk, Bonventre JV. Acute Kidney Injury. Ann Rev Med 2016;14;67:293-307

[65] Basile DP, Fredrich K, Chelladurai B, Leonard EC, Parrish AR. Renal ischemia reperfusion inhibits VEGF expression and induces ADAMTS-1, a novel VEGF inhibitor. Am J Physiol Renal Physiol 2008;294:F928-936

[66] Basile DP, Donohoe D, Roethe K, Osborn JL. Renal ischemic injury results in permanent damage to peritubular capillaris and influences long-term function. Am J Physiol Ren Physiol 2001;281:F887-99

[67] Zuk A, Bonventre JV, Brown D, Matlin KS. Polarity, integrin, and extracellular matrix dynamics in the postischemic rat kidney. Am J Physiol 1998;275:C711-731

[68] Thadhani, Pascual M, Bonventre JV.. Acute renal failure. NEJM 1996:334:1448-1460

[69] Yang L, Besschetnova TY, Brooks CR, Shah JV, Bonventre JV. Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. Nat Med 2010;16:535-543

[70] Bonventre JV , Zuk A. Ischemic acute renal failure: an inflammatory disease? Kidney Int 2004;66:480-485

[71] Li L, Okusa MD. Macrophages, dendritic cells, and kidney ischemia-reperfusion injury. Semin Nephrol 2010;30:268-277

[72] Ricardo SD, van Goor H, Eddy A.. Macrophage diversity in renal injury and repair. J Clin Invest 2008;118:3522-3530.

[73] Bonventre JV. Dedifferentiation and proliferation of surviving epithelial cells in acute renal failure. JASN 2003;14(Supple1):S55-6

[74] Humphreys BD, Valerius MT, Kobayashi A, Mugford JW, Soeung S, Duffield JS, McMahon AP, Bonventre JV. Intrinsic epithelial cells repair the kidney after injury. Cell Stem Cell 2008;2:284-291

[75] Venkatachalam MA, Griffin KA, Lan R, Geng H, Saikumar P, Bidani AK. AKI: a springboard for progression in CKD. Am J Physiol Renal Physiol 2010

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3. Clinical consequences of acute kidney injury

The recent paradigm shift that patients die of AKI rather than with AKI is based on epidemiological data demonstrating the association between AKI and mortality. In the following article the clinical consequences of AKI are summarized, this may help explain the association between AKI and mortality.

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PUBLISHED IN
Contrib Nephrol.
Basel, Karger, 2011;174-56-64

ABSTRACT

AKI can no longer be considered a surrogate marker for severity of illness. Recent epidemiologic data demonstrate the association of AKI and mortality. Even small decreases of kidney function are associated with increased mortality. Several clinical consequences of AKI may explain the association of AKI and mortality. Decreased free water clearance leading to volume overload contributes to morbidity and mortality but also to deterioration of kidney function. Acid base disorders and electrolyte abnormalities interfere with normal functioning of many processes in the body. Critically ill patients have an increased prevalence of infection. Infection and antimicrobial therapy can be the cause of AKI, but infection can also be a consequence of AKI. Finally, inadequate antimicrobial dosing probably plays an important role in morbidity and mortality of AKI. These findings lead to a paradigm shift: Patients die because of AKI, rather than with AKI.

3.1 INTRODUCTION

In the past, AKI was considered a surrogate marker for severity of illness, and patient mortality was considered a consequence of the underlying disease [1]. Especially in ICU patients, AKI develops as a consequence of other disease, e.g. sepsis, cardiogenic shock or trauma, that in a certain number of patients will lead to mortality. However, there is an abundance of epidemiologic data that demonstrates that AKI itself also contributes to higher mortality. This is so for the most severe form of AKI, where patients are treated with RRT [2-6]. Small decreases of kidney function are also associated with increased short-term mortality (hospital and 28-day). This has been demonstrated in various settings such as in contrast induced-AKI (CI-AKI), in patients who underwent cardiac surgery, in hospitalized patients and in ICU patients [7-12]. When AKI is classified according to the newly developed sensitive RIFLE or AKI classification, all studies demonstrated an association with hospital mortality [5, 13-15]. Other outcomes, such as length of hospital stay, readmission rate, development of end stage kidney disease, and long term (1-10 year) mortality are also affected by severe and less severe episodes of AKI during ICU stay [16-21]. In this overview we will discuss clinical consequences of AKI that may explain the association of AKI and mortality (Fig. 1).

3.2 MORBIDITY CAUSED BY AKI

3.2.1 Fluid overload Fluid resuscitation is one of the cornerstones for treatment of ICU patients with an episode of oliguria or developing AKI. The majority of AKI patients, especially those with severe AKI, will have decreased (free) water clearance. This will lead to accumulation of water, and several observational studies found that this is associated with worse outcome [22-24]. It is difficult to delineate whether fluid overload is only a surrogate marker of severity of illness or if it is in itself the cause of increased morbidity and mortality. Some arguments are in favour for the latter.

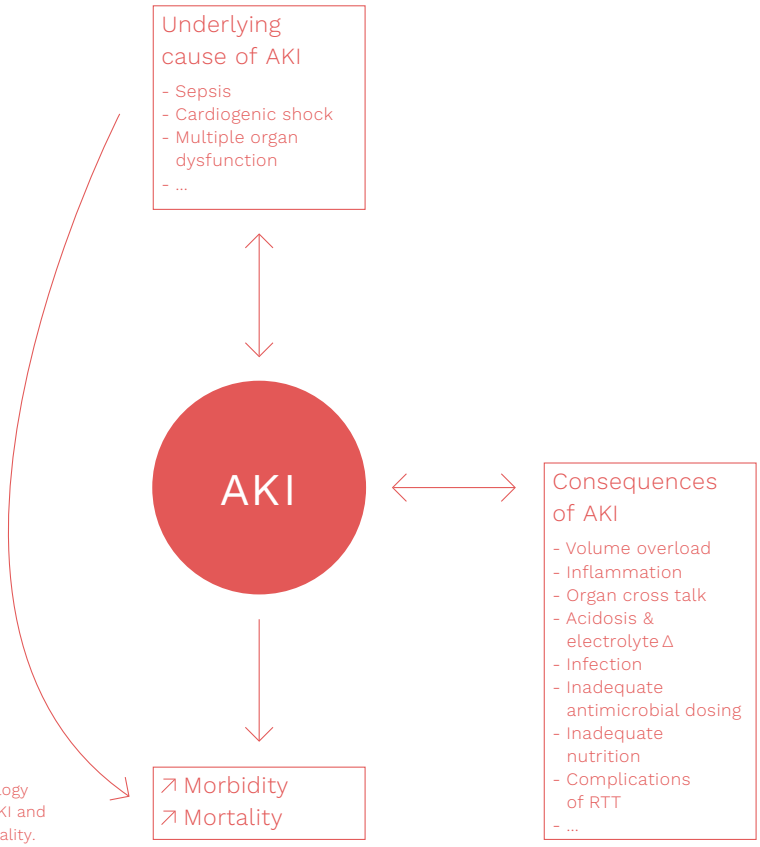

Fig. 1.

Patients are dying of AKI and not with AKI.

The interaction between the aetiology of AKI and the consequences of AKI and the impact on morbidity and mortality.

Fluid overload may lead to a series of minor and major complications that may influence outcome. It may result in a broad range of complication such as development of tissue oedema, ascites and eventually intra-abdominal hypertension and abdominal compartment syndrome, pleural effusion and pulmonary oedema [25]. An elegant demonstration of the untoward effects of increased total body water was in a prospective study on patients who underwent colorectal surgery, and who were randomized to a restrictive and a normal peri-operative fluid regimen [26]. Patients who were randomized to the restrictive fluid regimen had significantly less complications, in particular cardiopulmonary complications, and better tissue healing.

Despite many AKI patients are already fluid overloaded, the majority of these patients will receive fluid boluses in order to restore effective arterial blood volume and restore pre-renal AKI. However, fluid overload may not only contribute to extra morbidity, but may also contribute to deterioration of kidney function. Especially, in cardiac patients, increased central venous pressure and right ventricular failure, is associated with development of AKI [27-29]. Also, in Acute Respiratory Distress Syndrome (ARDS), randomisation to a restrictive fluid therapy regimen resulted in less need for renal replacement therapy (10% versus 14%, p = 0.06) [30]. Another mechanism by which fluid overload may lead to AKI is through development of intra-abdominal hypertension, abdominal compartment syndrome (ACS), by decreased thoracic and abdominal wall compliance, retroperitoneal oedema and ascites [25, 31, 32].

3.2.2 Inflammation and "organ cross talk" AKI is characterised by a profound inflammatory reaction in the kidneys and in the systemic circulation. This systemic inflammatory response leads to dysfunction of other organs. Animal experiments demonstrated that AKI leads to gene activation of pro-inflammatory and anti-inflammatory mediators in the lung, which results in ARDS, with exudation of albumin in the alveoli, changes of aquaporins and sodium channels and infiltration of neutrophils [33-40]. Acid base disorders, which are commonly seen in AKI, also play a role in this inflammatory reaction. Hyperchloremic acidosis is associated with an increased interleukin (IL)-6/IL-10 ratio with a resultant pro-inflammatory effect, while lactic acidosis will decrease both IL-6 and IL-10 resulting in an anti-inflammatory status [41-43]. A more extensive discussion on this topic can be found in other chapters in this issue of *"Contributions to Nephrology"*.

3.2.3 Acidosis The kidneys play an important role in acid-base homeostasis. Metabolic acidosis is the resultant of accumulation of anions such as chloride, phosphate, and other anions that are not routinely measured [44,45]. Acidosis occurs in up to one-third of patients who are initiated on RRT [46]. Acidosis interferes with normal functioning of many processes in the body. It will lead to hemodynamic instability by decreased cardiac output and vasodilatation. Decreased density of β-receptors at the cell surface of the myocardium, interference with intracellular calcium handling, increased nitric oxide production and interference with the inflammatory response are the mechanisms that most likely play a role in this [41,42,47-49]. Further, different aetiology of acidosis is associated with different systemic effects [41-43]. Moderate hyperchloremic acidosis is associated with an increased NO production, leading to vasodilatation, while in lactic acidosis there is a gradual decline in NO production.

3.2.4 Electrolyte abnormalities Also the kidney regulates electrolyte homeostasis. Up to one third of patients with severe AKI will develop dilution hyponatremia by decreased free water clearance [50, 51]. Hyponatremia is associated with severe complications such as cerebral oedema, and with worse outcomes [52, 53]. Furthermore, between 6,1% and one third of the patients who are initiated on RRT develop hyperkalemia, a condition that is associated with arrhytmias and death [46,50].

3.2.5 Infection Infection and antimicrobial therapy for infection play a central role in the course of AKI [54]. ICU patients with AKI have an increased prevalence of

infection [54-58]. Infection and antimicrobial therapy may be the cause of AKI, but infection may also be a resultant of AKI. In a series in our centre we found that 80.2% of ICU patients who had AKI and were treated with RRT, were also treated for infection [55]. 37,5% of the patients even had two ore more episodes of infection. Almost half of these infections started just before initiation of RRT, 40% during RRT and approximately 10% in the period immediately after discontinuation of RRT. Several factors may play a role in this interplay between infection, antimicrobial therapy and AKI.

3.2.6 Inadequate antimicrobial therapy
Adequate prescription of antimicrobial therapy is a challenge in ICU patients. The volume of distribution, metabolization and clearance can have important variations among patients and also within the same patient in different time periods of ICU stay. This may result in underdosing and overdosing of antimicrobials when standard antimicrobial dosing schedules are used.

Correct dosing is even more difficult in AKI patients. A first issue is correct evaluation of kidney function. Formulas that are used for assessment of kidney function in patients with chronic kidney disease, such as the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations were validated in non-ICU patients with moderate chronic kidney disease and are based on serum creatinine, and variables such as age, body eight and gender. These equations are not adequate for assessment of kidney function in ICU patients [59, 60].

Kidney function is best assessed by measurement of urinary creatinine clearance, i.e. (= (urine volume) x (urine creatinine concentration) / (time in minutes) x (serum creatinine concentration)). This calculation requires exact timing and measurement of urine volume, and a stable kidney function during the measurement period. As this condition is seldom met in patients with AKI, one can shorten the measurement period to, for example, 2 or 4 h, or use the mean of serum creatinine concentration measured just before and after the measurement period [60].

Another issue that precludes correct dosing of antimicrobial therapy in ICU patients who have AKI, is that dosing schedules for antimicrobial therapy are most based on data from patients with chronic kidney disease. These are not necessarily useful in ICU patients with AKI and comparable degree of GFR. Serum concentration can be lower in ICU patients by increased volume of distribution, decreased gastro intestinal absorption, increased GFR during treatment, or RRT. Examples of factors that may increase serum concentrations are decreased albumin concentration, decreased kidney function and periods without RRT.

In patients treated with RRT, dosing schedules are available. But variables as dialysis blood flow, dialysate flow, ultrafiltration rate, administration of pre- or postdilution, filter characteristics, may vary from centre to center, and have impact on dialysis dose and so on clearance.

3.2.7 Inadequate metabolic and nutritional support ICU patients with AKI are usually in a catabolic state, and treatment with RRT leads to additional losses of amino acids and proteins. Loss of phosphorus in CRRT can lead to prolonged time on mechanical ventilation [61]. Further, the concentration of trace elements can be lower as a resultant of acute phase reaction, losses of fluids, and removal by RRT. Finally, water-soluble vitamins such as vitamins C, thiamine and folic acid are removed by RRT [62].

At present, the data on the effects of nutritional interventions and different RRT modalities on nutritional status and blood concentration of trace elements and vitamins in ICU patients with AKI are insufficient. Given the data that we do know, and given the vast evidence on the importance of nutritional status and nutritional interventions in chronic haemodialysis patients and in ICU patients in general, this aspect of care needs further exploration.

3.3 CONCLUSION

Current epidemiologic findings demonstrate the strong association between AKI and short-term and long-term mortality. A whole range of clinical complications

of AKI help to explain this. Factors that may help explain increased morbidity and mortality in AKI patients are a consequence of decreased kidney function such as volume overload, acidosis and electrolyte abnormalities. AKI may also impact on other organs, as in organ crosstalk between kidneys and lungs. AKI patients have an increased incidence of infection. Infection may impact on mortality, but also, inadequate antimicrobial therapy may play an important role. Current dosing recommendations for antimicrobials are most inadequate for ICU patients who have AKI, and adequate dosing is therefore a topic that needs further study. Finally, nutritional support is an underemphasized aspect of care for AKI patients in the ICU. Especially in AKI patients treated with RRT, we need more data on nutrition and supplementation of trace elements and vitamins.

The paradigm shift that patients die of, rather than with AKI, emphasizes the need for early recognition of AKI or clinical circumstances that eventually can lead to the development of AKI. RIFLE and AKIN criteria can be useful tools for intensivists in the early identification and management of AKI. The prevention of AKI in critically ill patients cannot be overemphasized. Adequate fluid therapy, the correction of acid base disorders and electrolyte imbalances, the early recognition of infections and adequate dosing of antimicrobial therapy are key issues in the management of AKI and in reducing its additional mortality in critically ill patients.

REFERENCES

[1] Kellum JA, Angus DC. Patients are dying of acute renal failure. Crit Care Med. 2002;30:2156-2157.

[2] Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med. 1998;104:343 - 348.

[3] Metnitz PG, Krenn CG, Steltzer H et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30:2051 - 2058.

[4] Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol. 2003;14:1022-1030.

[5] Hoste EAJ, Schurgers M. Epidemiology of AKI: How big is the problem? Crit Care Med. 2008;36:S1-4.

[6] Elseviers MM, Lins RL, Van der Niepen P et al. Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. Crit Care. 2010;14:R221.

[7] Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. JAMA. 1996;275:1489-1494.

[8] Lassnigg A, Schmidlin D, Mouhieddine M et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol. 2004;15:1597-1605.

[9] Lassnigg A, Schmid ER, Hiesmayr M et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? Crit Care Med. 2008;36:1129-1137.

[10] Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients.

J Am Soc Nephrol. 2005;16:3365-3370.

[11] Liangos O, Wald R, O'Bell JW, Price L, Pereira A, Jaber BL. Epidemiology and outcomes of acute renal failure in hospitalized patients: A national survey. Clin J Am Soc Nephrol. 2006;1:43-51.

[12] Thakar CVMDF, Christianson AMS, Freyberg RMS, Almenoff PMD, Render MLMD. Incidence and outcomes of acute kidney injury in intensive care units: A Veterans Administration study. Critical Care Medicine. 2009;37:2552-2558.

[13] Hoste EA, Clermont G, Kersten A et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10:R73.

[14] Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. Kidney Int. 2008;73:538 - 546.

[15] Brusselaers N, Monstrey S, Colpaert K, Decruyenaere J, Blot SI, Hoste EA. Outcome of acute kidney injury in severe burns: a systematic review and meta-analysis. Intensive Care Med. 2010;36:915-925.

[16] Ishani A, Xue JL, Himmelfarb J et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20:223-228.

[17] Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. Am J Kidney Dis. 2007;50:712-720.

[18] Bihorac A, Yavas S, Subbiah S et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. Ann Surg. 2009;249:851-858.

[19] Hobson CE, Yavas S, Segal MS et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation. 2009;119:2444-2453.

[20] Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol. 2010;21:345-352.

[21] Logeart D, Tabet JY, Hittinger L et al. Transient worsening of renal function during hospitalization for acute heart failure alters outcome. Int J Cardiol. 2008;127:228-232.

[22] Payen D, de Pont A, Sakr Y et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Critical Care. 2008;12:R74.

[23] Bouchard J, Soroko SB, Chertow GM et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009

[24] Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD. Fluid Balance, Diuretic Use, and Mortality in Acute Kidney Injury. Clin J Am Soc Nephrol. 2011

[25] De Waele JJ, De Laet I, Kirkpatrick AW, Hoste E. Intra-abdominal Hypertension and Abdominal Compartment Syndrome. Am J Kidney Dis. 2011;57:159-169.

[26] Brandstrup B, Tonnesen H, Beier-Holgersen R et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2003;238:641-648.

[27] Testani JM, Khera AV, St John Sutton MG et al. Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. Am J Cardiol. 2010;105:511-516.

[28] Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential Effects of Aggressive Decongestion During the Treatment of Decompensated Heart Failure on Renal Function and Survival. Circulation. 2010

[29] Mullens W, Abrahams Z, Francis GS et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589-596.

[30] Wiedemann HP, Wheeler AP, Bernard GR et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354:2564-2575.

[31] Dalfino L, Tullo L, Donadio I, Malcangi V, Brienza N. Intra-abdominal hypertension and acute renal failure in critically ill patients. Intensive Care Med. 2008;34:707-713.

[32] De Waele JJ, De Laet I. Intra-abdominal hypertension and the effect on renal function. Acta Clin Belg Suppl. 2007;371-374.

[33] Grigoryev DN, Liu M, Hassoun HT, Cheadle C, Barnes KC, Rabb H. The local and systemic inflammatory transcriptome after acute kidney injury. J Am Soc Nephrol. 2008;19:547-558.

[34] Hassoun HT, Grigoryev DN, Lie ML et al. Ischemic acute kidney injury induces a distant organ functional and genomic response distinguishable from bilateral nephrectomy. Am J Physiol Renal Physiol. 2007;293:F30-40.

[35] Hoke TS, Douglas IS, Klein CL et al. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. J Am Soc Nephrol. 2007;18:155-164.

[36] Kim DJ, Park SH, Sheen MR et al. Comparison of Experimental Lung Injury from Acute Renal Failure with Injury due to Sepsis. Respiration. 2006;73:815-824.

[37] Ko GJ, Rabb H, Hassoun HT. Kidney-lung crosstalk in the critically ill patient. Blood Purif. 2009;28:75-83.

[38] Kramer AA, Postler G, Salhab KF, Mendez C, Carey LC, Rabb H. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. Kidney Int. 1999;55:2362-2367.

[39] Rabb H, Chamoun F, Hotchkiss J. Molecular mechanisms underlying combined kidney-lung dysfunction during acute renal failure. Contrib Nephrol. 2001;41-52.

[40] Rabb H, Wang Z, Nemoto T, Hotchkiss J, Yokota N, Soleimani M. Acute renal failure leads to dysregulation of lung salt and water channels. Kidney Int. 2003;63:600-606.

[41] Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. Chest. 2004;125:243-248.

[42] Kellum JA, Song M, Li J. Science review: extracellular acidosis and the immune response: clinical and physiologic implications. Crit Care. 2004;8:331-336.

[42] Kellum JA, Song M, Li J: Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. Am J Physiol Regul Integr Comp Physiol 2004;286:R686-R692.

[44] Rocktaeschel J, Morimatsu H, Uchino S et al. Acid-base status of critically ill patients with acute renal failure: analysis based on Stewart-Figge methodology. Crit Care. 2003;7:R60.

[45] Forni LG, McKinnon W, Lord GA, Treacher DF, Peron JM, Hilton PJ. Circulating anions usually associated with the Krebs cycle in patients with metabolic acidosis. Crit Care. 2005;9:R591-5.

[46] Bellomo R, Cass A,

Cole L et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361:1627-1638.

[47] Kellum JA, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. Chest. 2006;130:962-967.

[48] Marsh JD, Margolis TI, Kim D. Mechanism of diminished contractile response to catecholamines during acidosis. Am J Physiol. 1988;254:H20-7.

[49] Nimmo AJ, Than N, Orchard CH, Whitaker EM. The effect of acidosis on beta-adrenergic receptors in ferret cardiac muscle. Exp Physiol. 1993;78:95-103.

[50] Uchino S, Bellomo R, Ronco C. Intermittent versus continuous renal replacement therapy in the ICU: impact on electrolyte and acid- base balance. Intensive Care Med. 2001;27:1037-1043.

[51] Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. Ann Intern Med. 1992;117:891-897.

[52] Funk GC, Lindner G, Druml W et al. Incidence and prognosis of dysnatremias present on ICU admission. Intensive Care Med. 2010;36:304-311.

[53] Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. Crit Care. 2008;12:R162.

[54] Vandijck DM, Reynvoet E, Blot SI, Vandecasteele E, Hoste EA. Severe infection, sepsis and acute kidney injury. Acta Clin Belg Suppl. 2007;332-336.

[55] Reynvoet E, Vandijck DM, Blot SI et al. Epidemiology of infection in critically ill patients with acute renal failure. Crit Care Med. 2009;37:2203-2209.

[56] Hoste EA, Vandijck DM, Vanholder RC et al. Health implications of antimicrobial resistance for patients with acute kidney injury and bloodstream infection. Infect Control Hosp Epidemiol. 2007;28:1107-1110.

[57] Hoste EA, Blot SI, Lameire NH, Vanholder RC, De Bacquer D, Colardyn FA. Effect of nosocomial bloodstream infection on the outcome of critically ill patients with acute renal failure treated with renal replacement therapy. J Am Soc Nephrol. 2004;15:454-462.

[58] Mehta RL, Bouchard J, Soroko SB et al. Sepsis as a cause and consequence of acute kidney injury: Program to Improve Care in Acute Renal Disease. Intensive Care Med. 2010

[59] Hoste EA, Damen J, Vanholder RC et al. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. Nephrol Dial Transplant. 2005;20:747-753.

[60] Lameire N, Hoste E. Reflections on the definition, classification, and diagnostic evaluation of acute renal failure. Curr Opin Crit Care. 2004;10:468-475.

[61] Demirjian S, Teo BW, Guzman JA et al. Hypophosphatemia during continuous hemodialysis is associated with prolonged respiratory failure in patients with acute kidney injury. Nephrol Dial Transplant. 2011

[62] Fiaccadori E, Regolisti G, Cabassi A. Specific nutritional problems in acute kidney injury, treated with non-dialysis and dialytic modalities. NDT Plus. 2009;3:1-7.

4. Management of acute kidney injury

4.1 PREVENTION OF ACUTE KIDNEY INJURY

AKI can no longer be considered a surrogate marker for severity of illness. The association between AKI and mortality emphasizes the need for early recognition and prevention of AKI. In the following article we summarized the KDIGO guidelines on AKI in critically ill patients. Special attention was paid to the KDIGO AKI bundle proposing measures for the prevention of AKI.

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PUBLISHED IN
Curr Opin Crit Care.
2013 Dec;19(6):544-53.

IMPLEMENTING THE KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES ACUTE KIDNEY INJURY GUIDELINES IN ICU PATIENTS.

ABSTRACT

Purpose of review AKI is a frequent complication in ICU patients, and is associated with adverse outcomes. With the purpose of improving outcome of AKI, the Kidney Disease: Improving Global Outcomes (KDIGO) group, a group of experts in critical care nephrology, has presented a set of guidelines in 2012, based on the evidence gathered until mid 2011. This review will update these guidelines with recent evidence.

Recent findings Early application of a set of therapeutic measures – a bundle – is advised for the prevention and therapy of AKI. Hemodynamic optimization remains the cornerstone of prevention and treatment of AKI. Fluid resuscitation should be with isotonic crystalloids. Recent evidence demonstrated a higher risk for RRT an mortality in hydroxyethyl starch-exposed patients. Further, blood pressure should be maintained by the use of vasopressors in vasomotor shock. Nephrotoxic drugs should be avoided or stopped when possible. Contrast-associated AKI should be prevented by prehydration with either NaCl 0.9% or a bicarbonate solution. Other therapies, including intravenous N-acetylcysteine and hemofiltration are not recommended. Optimal timing of RRT remains controversial. Fluid overload remains an important determinant for the initiation of RRT. Continuous therapies are preferred in hemodynamically unstable patients; otherwise choice of modality does not impact on outcomes.

Summary The KDIGO guidelines as presented in 2012 provide guidelines on the domain of definition of AKI, prevention and treatment, contrast-induced AKI and dialysis interventions for AKI. Especially, early application of a set of measures, the AKI bundle may prevent AKI and improve outcome.

4.1.1 Introduction Acute kidney injury (AKI) is a frequent complication in ICU patients, and is associated with worse outcomes. When it is defined by the sensitive RIFLE definition for AKI or its modifications, the Acute Kidney Injury Network (AKIN) or Kidney Disease: Improving Global Outcomes (KDIGO) definitions for AKI, it occurs in one-third to two-thirds of ICU patients [1-8]. Approximately 5 to 10 % of ICU patients are treated with renal replacement therapy (RRT) for AKI [9-11]. AKI is associated with worse outcomes such as, longer length of ICU and hospital stay, short-term survival (e.g. 28 d, ICU or hospital survival), also long-term survival (up to 10 years follow-up), development of chronic kidney disease (CKD) and end stage renal disease (ESRD), and therefore increased use of resources and costs.

Table 1.

Definition and classification of AKI

A. AKI is defined by either an increase of sCr or an episode of oliguria

Increase of sCr >0.3 mg/dL within 48-hours, or
Increase of sCr by >1.5-fold above baseline,
know or assumed to have occurred within 7days, or
Urine volume < 0.5 mL/kg/h for 6 hours.

B. AKI severity is staged by the worst of either sCr changes or oliguria

	SCR	URINE OUTPUT
STAGE 1	≥ 1.5 to 1.9 times baseline OR ≥ 0.3 mg/dL increase	<0.5 mL/kg/h for 6-12 h
STAGE 2	≥ 2.0 to 2.9 times baseline	<0.5 mL/kg/h for ≥12 h
STAGE 3	≥ 3.0 times baseline OR Increase of sCr to ≥ 4.0 mg/dL OR RRT OR In patients <18y, decrease	<0.3 mL/kg/h for ≥ 24 h OR Anuria for ≥12 h

Despite decades of research, and dozens of compounds evaluated, there are at present still very little therapeutic options for treatment or prevention of AKI. Explanations for this may be the heterogenous and multifactorial cause.

Despite the absence of specific therapies for AKI, outcome has improved over years [12, 13]. This may be explained by improvement of therapy for associated disease, and increased awareness of specific nephrology issues. Several studies showed that simple "kidney-friendly" interventions (e.g. stopping of nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), and early correction of volume status), resulted in less (severe) AKI, and better outcomes [14-19]. Therefore, the guidelines that were issued by the KDIGO group are of great importance for advances in the treatment of AKI. This process was conducted by a group of experts, using an evidence-based methodology and the Grading of Recommendations Assessment, Development and Evaluation system. As the amount of guidelines is too large to cover them all in this article, we will highlight those that are most pertinent for everyday practice.

4.1.2 Definition of AKI An important accomplishment of the last decade was the introduction by the Acute Dialysis Quality Initiative (ADQI) of the RIFLE consensus definition for AKI [1]. It allows comparisons between studies, interventions in AKI patient cohort with similar severity stage, and as it also defines very early AKI with low severity, it allows early intervention. This definition was later modified, first by the Acute Kidney Injury Network (AKIN) [2], and recently by KDIGO [3]. AKI is defined by either an increase of serum creatinine (sCr) or an episode of decreased urine output (UO) (Table 1). Importantly, a patient needs to fulfill only one of the criteria for the definition of AKI. Subsequently, the severity of AKI can be graded into one of 3 severity grades. There are some issues in this definition that needs extra discussion.

4.1.3 Timing As the emphasis is on acute deterioration of kidney function, the

patients should fulfill the criteria within a limited time frame. Therefore, one should compare a new sCr measurement to all sCr measurements in the preceding 7-day period for the 50% of increase of sCr, or 48 h for the 0.3 mg/dl sCr increase. If the increase of sCr takes place over a longer period the patient may be classified as having acute kidney disease. Of note, this time frame is only for the definition of AKI, and is not applicable for the staging of the AKI severity grade.

4.1.4 Baseline and reference serum creatinine When a patient has no sCr measurements available during the preceding 7-day period, one may use the baseline sCr concentration as a reference sCr for the 50% or greater increase of sCr, if this is presumed to have occurred within the prior 7 days. For the 0.3 mg/dL or greater increase of sCr, one needs a documented increase; therefore, the presumed baseline sCr may not be used for this. In patients who are in stable condition, ADQI recommended baseline sCr concentration may be obtained within a 3-month period preceding the current event [20]. Clinical judgment is essential for the correct estimation of this baseline sCr. For instance, if a baseline sCr is obtained at the end of a preceding ICU admission, it is very unlikely that this value represents true baseline kidney function. Also, assessment on whether the acute condition of AKI occurred within a 7-day period may be challenging. When there is no baseline sCr measurement available, the ADQI group advocated the use of the MDRD equation when there is an assumed baseline glomerular filtration rate (GFR) of 75 mL/min or greater [1]. The MDRD equation estimates GFR on gender, age, race, and sCr. This method has obviously limitations. The equation was validated in a cohort of US patients, and is therefore not applicable in patients with different body composition such as in Asia, or as in patients with lower muscle mass, e.g. as in critical illness, cirrhosis or paraplegia. Also, it is less precise in patients who have GFR>60 mL/min. Despite its shortcomings, this MDRD-based estimation of baseline sCr proved reasonably well in a cohort of ICU patients recruited in 3 centers in the USA [21]. Alternatively, baseline sCr may be estimated by use of multiple imputation method [22]. These single center data need to be confirmed in other settings, and although more precise, the complexity of this method may limits its use in daily practice.

4.1.5 Urine output criteria The definition requires that urine output is less than 0.5 ml/kg every hour for a 6 period. This limits its use to ICU patients with a urinary catheter. Studies have used variants of the original urine output criteria, e.g. urine output less than 3 ml/kg in a period of 6 hours, use of fixed blocks of 6 or 8 hours similar to the nurses' shift, back calculation of 24-h urine output and so on [23]. There is no indication what patient weight one should use for the oliguria criterion. It seems reasonable to use the "baseline" patients' weight, as actual patient weight in critically ill patients is seldom measured, and varies according to fluid overload, muscle wasting and weight loss secondary to critically illness. In morbidly obese, antibiotic dosing is recommended according to adjusted body weight. Although, this may also be reasonable for the definition of AKI, there are no data to support this.

4.1.6 Prevention and treatment of acute kidney injury This section describes a set of measures that are often described as the "AKI bundle" (Fig. 1). Summary of the KDIGO recommendations for the prevention and treatment of AKI are as follows:

1. Hemodynamic management
    a. Isotonic crystalloids rather than colloids
    b. Vasopressors in conjunction with fluids
    c. Protocol-based management of hemodialysis and oxygenation in perioperative setting or septic shock
2. Metabolism
    a. Target blood glucose at 110-149 mg/dl
    b. Energy intake of 20-30 kcal/kg per day
    c. Preferable enteral route
    d. Avoid protein restriction
        i. 0.8-1.0 g/kg per day of protein in non-catabolic AKI without RRT

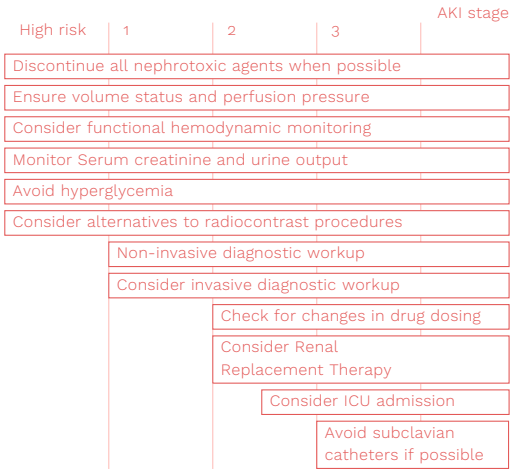
ii. 1.0-1.5 g/kg per day of protein in AKI on RRT, up to 1.7 g kg per day in patients on continuous renal replacement therapy (CRRT) and hypercatabolic patients.

3. Pharmacological management
   a. No diuretics for the prevention or treatment of AKI
   b. No dopamine for the prevention or treatment of AKI
   c. No fenoldopam for the prevention or treatment of AKI
   d. No N-acetylcysteine (NAC) for prevention of AKI in hypotension and postsurgery
   e. No atrial natriuretic peptide for the prevention or treatment of AKI
   f. No recombinant human insulin growth factor-1 for the prevention or treatment of AKI
   g. No aminoglycosides unless no suitable, less nephrotoxic alternatives are availbale
      i. Aminoglycosides: once daily
      ii. Monitor drug level in multiple dosing after 24 h, and in once daily dosing when more than 48h
      iii. Use topical or local instead of intravenous
   h. Amphotericine B:
      i. Lipid formulations
      ii. Prefer azoles/echinocandins
4. Nonpharmacological management
   a. Off-pump coronary artery bypass surgery not for AKI reasons
5. Contrast-induced AKI (CI-AKI)
   a. Define CI-AKI according to the KDIGO definition
   b. Assess risk for CI-Aki
   c. Consider not using contrast
   d. Use low-osmolar or iso-osmolar contrast
   e. Prehydrate and posthydrate with saline or bicarbonate solution
   f. Oral NAC, no intravenous N-acetylcysteine (IV NAC)
   g. Insufficient data on fenoldopam and theophylline
   h. No RRT

Bundles such as these are attractive and successful as these guarantee that all patients receive care according to the best evidence available. These allow healthcare workers, physicians and nurses to simply tick the measures that need to be done in patients at risk. Implementation of these care bundles has proven to improve the outcomes for instance sepsis [24,25]. Also, several studies in AKI patients have demonstrated that early implementation of simple measures by content experts improved outcomes [14-19].

Fig. 1.

The KDIGO AKI bundle: AKI-stage based management (after [3]).



4.1.7 Hemodynamic support

Guideline 3.1.1 "In the absence of hemorrhagic shock, we suggest using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for AKI or with AKI (2B)."

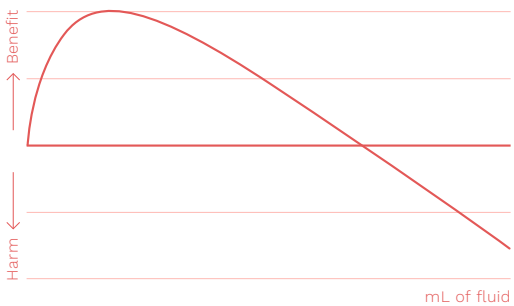
As colloids remain in the intravascular compartment for a longer period of time compared to crystalloids, they may seem attractive. However, older hydroxyethyl starch (HES) solutions showed nephrotoxicity, and observational data on gelatin containing solutions, suggest that these solutions have similar risk for nephrotoxicity [26,27]. Two well-designed studies on modern HES solutions with presumably less nephrotoxicity, further addressed this topic. The 6S trial included 798 critically ill patients with severe sepsis or septic shock. They compared a potato based 6% HES formulation with 130 kD molecular weight (6% HES 130) to Ringer's acetate [28]. At 90 days patients treated with HES had an increased mortality and a higher prevalence of RRT. The Crystalloid versus HydroxyEthyl Starch Trial included 7,000 general ICU patients and compared a corn-based 6% HES 130 formulation with 0.9% saline [29]. At 90 days the investigators found a lower incidence of AKI in HES treated patients compared with saline; however, there was a greater use of RRT in the HES group. There was no difference in mortality between both groups. Several meta-analyses have been published since. In a meta-analysis, including older and newer types of HES solutions, HES treatment was associated with increased mortality and AKI [30]. Two other meta-analyses on the new HES 130 solutions only, in all type of critically ill patients and in severe sepsis, found higher risk for RRT and mortality in HES exposed patients [31, 32]. On the basis of currently available evidence the US Food and Drug Administration (FDA), issued a boxed warning on the drug's label that HES solutions should not be used in critically ill patients. Also, the European Medicine Agency (EMA) suspended the marketing authorization for HES formulations, and started a new review on its use (www.bit.ly/2gC8lLE, accessed July 22nd, 2013).

The guideline also advises against the use of albumin, this was because the greater cost of this fluid is not associated with greater need for RRT. Unfortunately, this study did not report on AKI defined by more sensitive criteria. Albumin treated patients had a less positive fluid balance compared to saline treated patients. As a positive fluid balance may impact occurrence of AKI and outcome, this may in fact be an argument in favor of the use of albumin [34-38].

It is important to notice that the guideline specifically mentions that isotonic crystalloid solutions should be used for volume resuscitation. Two large studies found that non-isotonic crystalloid solutions containing high concentrations of chloride, such as in NaCl 0.9%, are associated with worse outcomes, including AKI, when compared to crystalloid solutions with lower chloride content such as Plasma-Lyte® (Baxter Healthcare Inc., Deerfield, Illinois, USA) [39,40]. These data illustrate that fluids should be seen as drugs with benefit, but also potential toxicity [41] (Fig. 2).

Fig. 2.

Relationship between fluid volume administered and beneficial and adverse effects.



Guideline 3.1.2 "We recommend the use of vasopressors in conjunction with fluids in patients with vasomotor shock with, or at risk for, AKI (1C)."

In critically ill patients, systemic hypotension may instigate a decreased renal perfusion eventually leading to AKI. To counter for this hypotensive state and to secure renal perfusion, vasopressor therapy is often used in these patients. In a state of vasomotor paralysis, the use of norepinephrine, an alpha-adrenergic agonist, has beneficial effects on renal blood flow and GFR [42-45].

Guideline 3.1.3 Protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting (2C) or in patients with septic shock.

Goal directed therapy has been studied extensively in the perioperative setting, and in meta-analysis, it was shown that this resulted in less postoperative AKI [46]. Although the beneficial effect of early goal-directed therapy (EGDT) in ICU patients on prevention of AKI is plausible, the evidence is still limited. The landmark study by Rivers et al. on EGDT for severe sepsis unfortunately reported no data on AKI [47]. In another study on EGDT in septic ICU patients by Lin et al., EGDT patients had a lower incidence of AKI compared to controls (38.9% vs. 55.2%, p = 0.015) [48]. At present several large multicenter studies on EGDT are under way that will provide additional evidence for its use.

4.1.8 Glycemic control and nutritional support AKI patients are severely catabolic and nutritional support is therefore an important aspect in the therapeutic plan for these patients. KDIGO summarized the available evidence on this topic and could only formulate recommendations with 2C or 2D grade of evidence, i.e. suggestions, with low or very low quality of evidence, mostly based upon expert opinion.

The landmark study of Van de Berghe and colleagues introduced the concept of intensive insulin therapy (IIT) in the ICU [49]. In surgical -, and a subgroup of medical ICU patients IIT protocol improved outcome and lowered the incidence of AKI [50,51]. These beneficial results could not be reproduced in subsequent studies on IIT [26,52]. One of the great concerns about IIT is the occurrence of hypoglycemia and its impact on outcome [53]. The KDIGO group suggests the use of a less stringent insulin therapy protocol targeting plasma glucose 110-149 mg/dL in critically ill patients.

On the basis of guidelines by expert panels, a total energy intake of 20-30 kcal/kg/d is suggested, preferably via enteral route. Proteins should not be restricted with the aim for preventing or delaying RRT. It is suggested to administer 0.8-1.0 g/kg/d in AKI patients not treated with RRT, and 1.0-1.5 g/kg/d in patients treated with RRT, up to 1.7 g/kg/d in patients treated with CRRT.

Guideline 3.4 We recommend not using diuretics to prevent or treat AKI, except in the management of fluid overload.

The available evidence from small studies cannot demonstrate that AKI is prevented with use of diuretics, or that AKI patients have faster recovery [54,55]. So far, diuretics only have a role in the management of volume overload.

Guideline 3.5 and 3.7: It is not recommend to use low-dose dopamine to prevent or treat AKI, similar it is suggested not to use fenoldopam or atrial natriuretic peptide to prevent or treat AKI.

Although vasodilation and increasing renal blood flow may seem a logic therapy for prevention and therapy of AKI, this has not been proven in studies. The evidence for being not beneficial is strongest for low-dose dopamine [56-58].

Guideline 3.6: Growth factor intervention.

Three observational studies in cardiac surgery found that erythropoietin (EPO) -treated patients prevented AKI [63-65]. However, these results could not be confirmed in an early

intervention study in ICU patients and in cardiac surgery patients [62,63]. KDIGO recommends therefore evaluating the usefulness of EPO in RCTs.

Guideline 3.8 Prevention of aminoglycoside- and amphotericin-related AKI

Given the nephrotoxicity of aminoglycosides and amphotericin, it is suggested to limit their use to infections where no alternative antimicrobial drug is available. Aminoglycosides should be administered preferably once daily, and drug levels should be monitored daily. Amphotericin should be given as a lipid formulation in order to reduce the nephrotoxicity.

4.1.9 Contrast-induced AKI Contrast media cause nephrotoxicity, but other risk factors for the development of AKI are often present in critically ill patients. For that reason, the term contrast associated AKI (CA-AKI) may seem more appropriate [64]. CA-AKI occurs in 10% to 22.5% of ICU patients, seldom requires RRT, and is associated with mortality, even on long-term follow up [64-68].

ICU patients should be assessed for risk for CA-AKI (pre-existing renal impairment, diabetes, nephrotoxic agents, advanced age, hemodynamic instability or hypertension). One should always consider not administering iodinated contrast. The lowest possible dose of modern low or iso-osmolar contrast agents should be used. Ideally NSAIDs, metformin, and diuretics are stopped one day on beforehand. In patients who are at risk for CA-AKI, intravenous volume expansion is recommended, either by administering saline (NaCl 0.9%) or a bicarbonate solution (846 mL Glucose 5% + 154 mL of 1000 mEg/L $NaHCO_3$) at a rate of 3 m/kg, for 1 h before and 1 mL/kg per hour for 6 h after contrast administration [69-72]. Although meta-analyses suggest benefit for the bicarbonate solution over saline, bias and heterogeneity limit this recommendation. In case the bicarbonate solution needs to be prepared, this may be associated with errors.

As the data on prevention of CA-AKI by N-acetycysteine (NAC) are conflicting, intravenous (IV) NAC is not recommended. But, given its beneficial potential and low toxicity, oral NAC should be administered in patients at risk for developing AKI. For most ICU patients, this seems less applicable, as most studies on oral NAC were performed in patients undergoing elective coronary angiography, with administration the night before contrast.

Evidence for the administration of fenoldopam or theophylline in patients at risk for AKI is lacking. Similarly, data supporting the prophylactic use of RRT in patients at increased risk for CA-AKI are insufficient.

4.1.10 Dialysis Interventions for treatment of AKI Although RRT has been in use for more than half a century, many aspects of this therapy remain controversial.

1. Timing and initiation of renal replacement therapy

It seems plausible that early initiation of RRT may positively impact on outcomes in ICU patients with AKI. But because of the possible side effects of this invasive therapy (hypotension, arrhythmia, hemorrhage, and complications of vascular access), there is a tendency to avoid RRT as long as possible. Also, RRT-induced hypoperfusion of the kidneys may impair kidney recovery and increase the progression of CKD [73].

Because of the lack of evidence, the KDIGO recommendations concerning timing of RRT in AKI are not graded. Initiation of RRT is advised in life-threatening changes in fluid, electrolyte and acid-base balance. Extracorporeal therapy can either function as renal replacement (when no kidney function is present) or renal support RRT (as an adjunct to kidney function). The following list shows potential applications for RRT:

1. Renal replacement: when there is no residual kidney function
    a. Life-threatening indications
        i. Hyperkalemia
        ii. Academia
        iii. Pulmonary edema
        iiii. Uremic complications (pericarditis, bleeding, etc)

b. Nonemergent indications
   i. Solute control
   ii. Fluid removal
   iii. Correction of acid-base abnormalities
2. Renal support: RRT is used as an adjunct
   a. Volume control
   b. Nutrition
   c. Drug delivery
   d. Regulation of acid-base and electrolyte status
   e. Solute modulation

Historically, timing of initiation of RRT was based on serum urea. However, serum urea is determined by many other variables that have no relation to kidney function [74]. In addition, recent studies could not demonstrate that urea differentiates between outcomes [75-77]. Metabolic acidosis is a complication that frequently occurs in ICU patients with AKI, but initiation of RRT in ICU patients with AKI and metabolic acidosis is still a matter of debate. As RRT does not treat the underlying cause of the acidosis, it can only provide restoration of homeostatic equilibrium and fluid balance, enabling specific therapeutic measures [78]. Numerous observational studies indicate fluid overload as an important determinant of worse outcomes [34-38]. Further, a subanalysis from the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL) study showed that a negative fluid balance during CRRT was associated with better survival [79]. Therefore fluid overload may be an important determinant for initiation of RRT. But also on this topic, prospective studies that randomized initiation of RRT based upon fluid status are absent.

2. Criteria for stopping renal replacement therapy

In literature, data considering the decision to stop RRT are even scarcer. Therefore KDIGO issues a pragmatic and non-graded recommendation that RRT should be discontinued when kidney function has recovered.

3. Anticoagulation

Patients without increased bleeding risk on intermittent RRT are recommended anticoagulation with unfractionated or low-molecular-weight heparin.

When CRRT is used, citrate anticoagulation is recommended, unless there are contra-indications for citrate such as reduced liver function or shock with reduced muscle perfusion. Data from five randomized studies showed that citrate based protocols were associated with longer filter life, less bleeding, and in 1 study also better survival [80-84]. Regional heparin anticoagulation, in which unfractionated heparin is neutralized after the filter with protamine is not advised. This is because the longer half-life of heparin makes it extremely difficult to titrate. In patients with heparin induced thrombocytopenia, heparin must be stopped, and thrombin inhibitors such as argatroban, or Factor Xa inhibitors (danaparoid or fondaparinux) are recommended.

4. Vascular access for renal replacement therapy in AKI

As in ESRD patients, central vein stenosis is more frequently seen in subclavian dialysis catheters [85,86], KDIGO recommends the right jugular vein, followed by the femoral vein as the optimal insertion place.

5. Modality of RRT in AKI patients

Generally, the choice of modality of RRT is based on the availability of a specific modality or local experiences. A Cochrane Collaboration meta-analysis including randomized controlled trials (RCT) that compared continuous RRT (CRRT) to intermittent hemodialysis (IHD) in AKI patients, could not demonstrate differences in hospital and ICU mortality, length of hospital stay or renal recovery [87,88]. CRRT and IHD should therefore be seen as complementary therapies except for patients with AKI who are hemodynamically unstable or present with increased intracranial pressure. In these cases, CRRT is considered the optimal modality of RRT.

6. Dose of renal replacement therapy in patients with AKI

The concept of dialysis dose is frequently addressed in literature. However, the

available evidence is limited and conflicting because of differences in study design and poor quality of reporting data [89]. Two recently published trials have assessed dialysis dose in critically ill patients with AKI. Both the RENAL and ATN trial compared high dose versus normal dose RRT and could not demonstrate differences in mortality or renal recovery [90,91]. On the basis of these data, KDIGO recommends in IHD and extended dialysis to deliver a weekly Kt/V of 3.9. For CRRT an effluent volume of 20-25 mL/kg/min is recommended. Because of downtime, this will require a higher prescription.

4.1.11 Conclusion The guidelines proposed by KDIGO propose an extensive overview of the current state of the art for AKI. The RIFLE and AKIN definitions for AKI have been modified into an updated version: the KDIGO definition and grading system. Similar to, for example, sepsis, early application of a bundle of measures is proposed for the prevention of AKI: the "KDIGO AKI bundle". These include avoidance of nephrotoxic agents, optimizing hemodynamic status, guidelines for the prevention of CA-AKI and guidelines for the processes of care for RRT.

ADDENDUM

Guideline 3.1.3 was predominantly based on the landmark study by Rivers et al [41]. However, three large randomized controlled trials were recently completed to reexamine the effect of EGDT on outcomes in patients with septic shock: the Protocolized Care for Early Septic Shock (ProCESS) trial conducted in the United States [93], the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial [94] and the Protocolized Management of Sepsis (ProMISe) trial in England [95]. These trials concluded that EGDT did not significantly decrease mortality in patients with septic shock compared with conventional care. In addition, an ancillary study to the ProCESS trial found no benefit for EGDT on renal outcome in terms of development or severity of AKI, administration of RRT and renal recovery [96].

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST

Eric A.J. Hoste received a speakers fee from Astute Medical, and has no other relevant conflicts of interest. W.D.C. has no conflicts of interest to declare.

REFERENCES

[1] Bellomo, R, C Ronco, JA Kellum, RL Mehta, P Palevsky: Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004, 8R204 -R 212.

[2] Mehta, RL, JA Kellum, SV Shah, BA Molitoris, C Ronco, DG Warnock, A Levin: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007, 11R31.

[3] Kidney disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical practice guideline for acute kidney injury. Kidney Int 2012, 21-138.

[4] Hoste, EA, M Schurgers: Epidemiology of acute kidney injury: how big is the problem? Crit Care Med 2008, 36S146-S151.

[5] Hoste, EA, G Clermont, A Kersten, R Venkataraman, DC Angus, D De Bacquer, JA Kellum: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006, 10R73.

[6] Ostermann, M, RW Chang: Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007, 351837-1843.

[7] Joannidis, M, B Metnitz, P Bauer, N Schusterschitz, R Moreno, W Druml, PG Metnitz: Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 2009, 351692-1702.

[8] Mandelbaum, T, DJ Scott, J Lee, RG Mark, A Malhotra, SS Waikar, MD Howell, D Talmor: Outcome of critically ill patients with acute kidney injury using the Acute Kidney Injury Network criteria. Crit Care Med 2011, 392659-2664.

[9] Metnitz, PG, CG Krenn, H Steltzer, T Lang, J Ploder, K Lenz, JR Le Gall, W Druml: Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 2002, 302051-2058.

[10] Uchino, S, JA Kellum, R Bellomo, GS Doig, H Morimatsu, S Morgera, M Schetz, I Tan, C Bouman, E Macedo et al.: Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005, 294813-818.

[11] Nisula, S, KM Kaukonen, ST Vaara, AM Korhonen, M Poukkanen, S Karlsson, M Haapio, O Inkinen, I Parviainen, R Suojaranta-Ylinen et al.: Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 2013, 39420-428.

[12] Bagshaw, SM, C George, R Bellomo: Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care 2007, 11R68.

[13] Waikar, SS, GC Curhan, R Wald, EP McCarthy, GM Chertow: Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol 2006, 171143-1150.

[14] Mehta, RL, B McDonald, F Gabbai, M Pahl, A Farkas, MT Pascual, S Zhuang, RM Kaplan, GM Chertow: Nephrology consultation in acute renal failure: does timing matter? Am J Med 2002, 113456-461.

[15] Perez-Valdivieso, JR, M Bes-Rastrollo, P Monedero, J de Irala, FJ Lavilla: Prognosis and serum creatinine levels in acute renal failure at the time of nephrology consultation: an observational cohort study. BMC Nephrol 2007, 814.

[16] Balasubramanian, G, Z Al-Aly, A Moiz, M Rauchman, Z Zhang, R Gopalakrishnan, S Balasubramanian, TM El-Achkar: Early nephrologist involvement in hospital-acquired acute kidney injury: a pilot study. Am J Kidney Dis 2011, 57228-234.

[17] Ponce, D, CD Zorzenon, NY Santos, AL Balbi: Early nephrology consultation can have impact on outcome of acute kidney injury patients. Nephrol Dial Transplant 2011, 263202-3206.

[18] Meier, P, RM Bonfils, B Vogt, B Burnand, M Burnier: Referral patterns and outcomes in noncritically ill patients with hospital-acquired acute kidney injury. Clin J Am Soc Nephrol 2011, 62215-2225.

[19] Colpaert, K, EA Hoste, K Steurbaut, D Benoit, S Van Hoecke, F De Turck, J Decruyenaere: Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. Crit Care Med 2012, 401164-1170.

[20] Hoste, EA, DN Cruz, A Davenport, RL Mehta, P Piccinni, C Tetta, G Viscovo, C Ronco: The epidemiology of cardiac surgery-associated acute kidney injury. Int J Artif Organs 2008, 31158-165.

[21] Zavada, J, E Hoste, R Cartin-Ceba, P Calzavacca, O Gajic, G Clermont, R Bellomo, JA Kellum: A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol Dial Transplant 2010, 253911-3918.

[22] Siew, ED, JF Peterson, SK Eden, KG Moons, TA Ikizler, ME Matheny: Use of Multiple Imputation Method to Improve Estimation of Missing Baseline Serum Creatinine in Acute Kidney Injury Research. Clin J Am Soc Nephrol 2013, 810-18.

[23] Macedo, E, R Malhotra, R Claure-Del Granado, P Fedullo, RL Mehta: Defining urine output criterion for acute kidney injury in critically ill patients. Nephrol Dial Transplant 2011, 26509-515.

[24] Levy, MM, RP Dellinger, SR Townsend, WT Linde-Zwirble, JC Marshall, J Bion, C Schorr, A Artigas, G Ramsay, R Beale et al.: The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Intensive Care Med 2010, 36222-231.

[25] O'Grady, NP, M Alexander, LA Burns, EP Dellinger, J Garland, SO Heard, PA Lipsett, H Masur, LA Mermel, ML Pearson et al.: Summary of recommendations: Guidelines for the Prevention of Intravascular Catheter-related Infections. Clin Infect Dis 2011, 521087-1099.

[26] Brunkhorst, FM, C Engel, F Bloos, A Meier-Hellmann, M Ragaller, N Weiler, O Moerer, M Gruendling, M Oppert, S Grond et al.: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008, 358125-139.

[27] Schabinski, F, J Oishi, F Tuche, A Luy, Y Sakr, D Bredle, C Hartog, K Reinhart: Effects of a predominantly hydroxyethyl starch (HES)-based and a predominantly non HES-based fluid therapy on renal function in surgical ICU patients. Intensive Care Med 2009, 351539-1547.

[28] Perner, A, N Haase, AB Guttormsen, J Tenhunen, G Klemenzson, A Aneman, KR Madsen, MH Moller, JM Elkjaer, LM Poulsen et al.: Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis. N Engl J Med 2012, 367124-134.

[29] Myburgh, JA, S Finfer, R Bellomo, L Billot, A Cass, D Gattas, P Glass, J Lipman, B Liu, C McArthur et al.: Hydroxyethyl Starch or Saline for

Fluid Resuscitation in Intensive Care. N Engl J Med 2012, 3671901-1911.

[30] Zarychanski, R, AM Abou-Setta, AF Turgeon, BL Houston, L McIntyre, JC Marshall, DA Fergusson: Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA 2013, 309678-688.

[31] Patel, A, U Waheed, SJ Brett: Randomised trials of 6 % tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: systematic review and meta-analysis. Intensive Care Med 2013, 39811-822.

[32] Gattas, DJ, A Dan, J Myburgh, L Billot, S Lo, S Finfer: Fluid resuscitation with 6 % hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med 2013, 39558-568.

[33] Finfer, S, R Bellomo, N Boyce, J French, J Myburgh, R Norton: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004, 3502247-2256.

[34] Payen, D, A de Pont, Y Sakr, C Spies, K Reinhart, J Vincent, I the Sepsis Occurrence in Acutely Ill Patients: A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Critical Care 2008, 12R74.

[35] Bouchard, J, SB Soroko, GM Chertow, J Himmelfarb, TA Ikizler, EP Paganini, RL Mehta: Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009,

[36] Vaara, ST, A-M Korhonen, K-M Kaukonen, S Nisula, O Inkinen, S Hoppu, JJ Laurila, L Mildh, M Reinikainen, V Lund et al.: Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012, 16R197.

[37] Teixeira, C, F Garzotto, P Piccinni, N Brienza, M Iannuzzi, S Gramaticopolo, F Forfori, M Rocco, C Ronco, C Belluomo Anello et al.: Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care 2013, 17R14.

[38] Grams, ME, MM Estrella, J Coresh, RG Brower, KD Liu: Fluid Balance, Diuretic Use, and Mortality in Acute Kidney Injury. Clin J Am Soc Nephrol 2011,

[39] Shaw, AD, SM Bagshaw, SL Goldstein, LA Scherer, M Duan, CR Schermer, JA Kellum: Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg 2012, 255821-829.

[40] Yunos, NM, R Bellomo, C Hegarty, D Story, L Ho, M Bailey: Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012, 3081566-1572.

[41] Murugan, R, JA Kellum: Fluid balance and outcome in acute kidney injury: is fluid really the best medicine? Crit Care Med 2012, 401970-1972.

[42] Di Giantomasso, D, R Bellomo, CN May: The haemodynamic and metabolic effects of epinephrine in experimental hyperdynamic septic shock. Intensive Care Med 2005, 31454-462.

[43] Di Giantomasso, D, H Morimatsu, CN May, R Bellomo: Intrarenal blood flow distribution in hyperdynamic septic shock: Effect of norepinephrine. Crit Care Med 2003, 312509-2513.

[44] Albanese, J, M Leone, F Garnier, A Bourgoin, F Antonini, C Martin: Renal effects of norepinephrine in septic and nonseptic patients. Chest 2004, 126534-539.

[45] Badin, J, T Boulain, S Ehrmann, M Skarzynski, A Bretagnol, J Buret, D Benzekri-Lefevre, E Mercier, I Runge, D Garot et al.: Relation between mean arterial pressure and renal function in the early phase of shock: a prospective, explorative cohort study. Crit Care 2011, 15R135.

[46] Brienza, N, MT Giglio, M Marucci, T Fiore: Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med 2009, 372079-2090.

[47] Rivers, E, B Nguyen, S Havstad, J Ressler, A Muzzin, B Knoblich, E Peterson, M Tomlanovich: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001, 3451368 - 1377.

[48] Lin, SM, CD Huang, HC Lin, CY Liu, CH Wang, HP Kuo: A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock 2006, 26551-557.

[49] Van den Berghe, G, P Wouters, F Weekers, C Verwaest, F Bruyninckx, M Schetz, D Vlasselaers, P Ferdinande, P Lauwers, R Bouillon: Intensive Insulin Therapy in Critically Ill Patients. N Engl J Med 2001, 3451359-1367.

[50] Van den Berghe, G, A Wilmer, G Hermans, W Meersseman, PJ Wouters, I Milants, E Van Wijngaerden, H Bobbaers, R Bouillon: Intensive insulin therapy in the medical ICU. N Engl J Med 2006, 354449-461.

[51] Schetz, M, I Vanhorebeek, PJ Wouters, A Wilmer, G Van den Berghe: Tight blood glucose control is renoprotective in critically ill patients. J Am Soc Nephrol 2008, 19571-578.

[52] Finfer, S, DR Chittock, SY Su, D Blair, D Foster, V Dhingra, R Bellomo, D Cook, P Dodek, WR Henderson et al.: Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009, 3601283-1297.

[53] Griesdale, DE, RJ de Souza, RM van Dam, DK Heyland, DJ Cook, A Malhotra, R Dhaliwal, WR Henderson, DR Chittock, S Finfer, D Talmor: Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009, 180821-827.

[54] Ho, KM, DJ Sheridan: Meta-analysis of frusemide to prevent or treat acute renal failure. Bmj 2006, 333420.

[55] Karajala, V, W Mansour, K J.A.: Diuretics in acute kidney injury. Minerva Anestesiol 2009, 75241-247.

[56] Bellomo, R, M Chapman, S Finfer, K Hickling, J Myburgh: Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000, 3562139-2143.

[57] Friedrich, JO, N Adhikari, MS Herridge, J Beyene: Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med 2005, 142510-524.

[58] Kellum, JA, J M Decker: Use of dopamine in acute renal failure: a meta-analysis. Crit Care Med 2001, 291526-1531.

[59] Tasanarong, A, S Duangchana, S Sumransurp, B Homvises, O Satdhabudha: Prophylaxis with Erythropoietin versus Placebo Reduces Acute Kidney Injury and Neutrophil Gelatinase-Associated Lipocalin in Patients Undergoing Cardiac Surgery: A Randomized,

Double-Blind Controlled Trial. BMC Nephrol 2013, 14136.

[60] Oh, SW, HJ Chin, DW Chae, KY Na: Erythropoietin improves long-term outcomes in patients with acute kidney injury after coronary artery bypass grafting. J Korean Med Sci 2012, 27506-511.

[61] Song, YR, T Lee, SJ You, HJ Chin, DW Chae, C Lim, KH Park, S Han, JH Kim, KY Na: Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery bypass grafting: a pilot study. Am J Nephrol 2009, 30253-260.

[62] de Seigneux, S, B Ponte, L Weiss, J Pugin, JA Romand, PY Martin, P Saudan: Epoetin administrated after cardiac surgery: effects on renal function and inflammation in a randomized controlled study. BMC Nephrol 2012, 13132.

[63] Endre, ZH, RJ Walker, JW Pickering, GM Shaw, CM Frampton, SJ Henderson, R Hutchison, JE Mehrtens, JM Robinson, JBW Schollum et al.: Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). Kidney Int 2010, 771020-1030.

[64] Hoste, EA, S Doom, J De Waele, LJ Delrue, L Defreyne, DD Benoit, J Decruyenaere: Epidemiology of contrast-associated acute kidney injury in ICU patients: a retrospective cohort analysis. Intensive Care Med 2011, 37271921-1931.

[65] Valette, X, JJ Parienti, B Plaud, P Lehoux, D Samba, JL Hanouz: Incidence, morbidity, and mortality of contrast-induced acute kidney injury in a surgical intensive care unit: A prospective cohort study. J Crit Care 2012,27 322

[66] Lakhal, K, S Ehrmann, A Chaari, JP Laissy, B Regnier, M Wolff, O Pajot: Acute Kidney Injury Network definition of contrast-induced nephropathy in the critically ill: Incidence and outcome. J Crit Care 2011, 26593-599.

[67] Rashid, AH, JL Brieva, B Stokes: Incidence of contrast-induced nephropathy in intensive care patients undergoing computerised tomography and prevalence of risk factors. Anaesth Intensive Care 2009, 37968-975.

[68] McCullough, PA: Contrast-Induced Acute Kidney Injury. J Am Coll Cardiol 2008, 511419-1428.

[69] Merten, GJ, WP Burgess, LV Gray, JH Holleman, TS Roush, GJ Kowalchuk, RM Bersin, A Van Moore, CA Simonton, III, RA Rittase et al.: Prevention of Contrast-Induced Nephropathy With Sodium Bicarbonate: A Randomized Controlled Trial. JAMA 2004, 2912328-2334.

[70] Hoste, EA, JJ De Waele, SA Gevaert, S Uchino, JA Kellum: Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis. Nephrol Dial Transplant 2010, 25747-758.

[71] Zoungas, S, T Ninomiya, R Huxley, A Cass, M Jardine, M Gallagher, A Patel, A Vasheghani-Farahani, G Sadigh, V Perkovic: Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Ann Intern Med 2009, 151631-638.

[72] Jang, J-S, H-Y Jin, J-S Seo, T-H Yang, D-K Kim, TH Kim, S-H Urm, D-S Kim, D-K Kim, S-H Seol et al.: Sodium Bicarbonate Therapy for the Prevention of Contrast-Induced Acute Kidney Injury. Circ J 2012, 762255-2265.

[73] Palevsky, PM, I Baldwin, A Davenport, S Goldstein, E Paganini: Renal replacement therapy and the kidney: minimizing the impact of renal replacement therapy on recovery of acute renal failure. Curr Opin Crit Care 2005, 11548-554.

[74] Waikar, SS, JV Bonventre: Can We Rely on Blood Urea Nitrogen as a Biomarker to Determine When to Initiate Dialysis? Clin J Am Soc Nephrol 2006, 1903-904.

[75] Bagshaw, SM, S Uchino, R Bellomo, H Morimatsu, S Morgera, M Schetz, I Tan, C Bouman, E Macedo, N Gibney et al.: Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. J Crit Care 2009, 24129 - 140.

[76] Ostermann, M, R Chang: Correlation between parameters at initiation of renal replacement therapy and outcome in patients with acute kidney injury. Critical Care 2009, 13R175.

[77] De Corte, W, R Vanholder, AW Dhondt, JJ De Waele, J Decruyenaere, C Danneels, S Claus, EA Hoste: Serum urea concentration is probably not related to outcome in ICU patients with AKI and renal replacement therapy. Nephrol Dial Transplant 2011, 263211-3218.

[78] Bellomo, R, M Lipcsey, P Calzavacca, M Haase, A Haase-Fielitz, E Licari, A Tee, L Cole, A Cass, S Finfer et al.: Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis. Intensive Care Med 2013,

[79] Bellomo, R, A Cass, L Cole, S Finfer, M Gallagher, J Lee, S Lo, C McArthur, S McGuiness, R Norton et al.: An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. Crit Care Med 2012, 401753-1760.

[80] Fealy, N, I Baldwin, M Johnstone, M Egi, R Bellomo: A pilot randomized controlled crossover study comparing regional heparinization to regional citrate anticoagulation for continuous venovenous hemofiltration. Int J Artif Organs 2007, 30301-307.

[81] Hetzel, GR, M Schmitz, H Wissing, W Ries, G Schott, PJ Heering, F Isgro, A Kribben, R Himmele, B Grabensee: Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrology Dialysis Transplantation 2011, 26232-239.

[82] Kutsogiannis, DJ, RT Gibney, D Stollery, J Gao: Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. Kidney Int 2005, 672361-2367.

[83] Monchi, M, D Berghmans, D Ledoux, JL Canivet, B Dubois, P Damas: Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. Intensive Care Med 2004, 30260-265.

[84] Oudemans-van Straaten, HM, RJ Bosman, M Koopmans, PH van der Voort, JP Wester, JI van der Spoel, LM Dijksman, DF Zandstra: Citrate anticoagulation for continuous venovenous hemofiltration. Crit Care Med 2009, 37545-552.

[85] Cimochowski, GE, E Worley, WE Rutherford, J Sartain, J Blondin, H Harter: Superiority of the internal jugular over the subclavian access for temporary dialysis. Nephron 1990, 54154-161.

[86] Schillinger, F, D Schillinger, R Montagnac, T Milcent: Post catheterisation vein stenosis in haemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular accesses. Nephrol Dial Transplant 1991, 6722-724.

[87] Rabindranath, K, J Adams, AM Macleod, N Muirhead: Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev 2007, CD003773.

[88] Schneider, AG, R Bellomo, SM Bagshaw, NJ Glassford, S Lo, M Jun, A Cass, M Gallagher: Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med 2013,

[89] Bagshaw, SM, R Bellomo, P Devarajan, C Johnson, CJ Karvellas, DJ Kutsiogiannis, R Mehta, N Pannu, A Romanovsky, G Sheinfeld et al.: Review article: Acute kidney injury in critical illness. Can J Anaesth 2010,

[90] Palevsky, PM, JH Zhang, TZ O'Connor, GM Chertow, ST Crowley, D Choudhury, K Finkel, JA Kellum, E Paganini, RM Schein et al.: Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008, 3597-20.

[91] Bellomo, R, A Cass, L Cole, S Finfer, M Gallagher, S Lo, C McArthur, S McGuinness, J Myburgh, R Norton et al.: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009, 3611627-1638.

[92] Process Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683–93.

[93] ARISE Investigators, Anzics Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–506.

[94] Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301–11.

[95] Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM,Pike FL, et al. ProCESS and ProGReSS-AKI Investigators. The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock. Am J Respir Crit Care Med. 2016 Feb 1;193(3):281-7.

4.2 RENAL REPLACEMENT THERAPY IN CRITICALLY ILL PATIENTS WITH ACUTE KIDNEY INJURY

Critically ill patients commonly suffer from multi-organ failure. The kidneys are often involved in such a syndrome. When AKI is severe, renal replacement therapy is routinely used in the ICU to treat severe AKI.

4.2.1. A brief history The concept of "dialysis" was first described in 1861 by the chemist Graham at the Anderson's University in Glasgow. He was able to extract urea from urine by diffusion through a vegetable parchment coated with albumin. The first artificial kidney was developed and tested on animals in 1913 by Abel and his colleagues at the John Hopkins University. The device passed blood from an arterial cannula through celluloid tubes which were contained in a glass jacket filled with saline or artificial serum. It was never used on humans. It was not until 1924 when the first human hemodialysis was performed in a uremic patient by Haas at the Giessen University in Germany. The dialysis lasted less than 15 minutes using a tubular device made of collodion (cellulose trinitrate). Hirudin was used for anticoagulation [1]. Dialysis as we know it today is based on the work by the Dutch physician Kolff who constructed an artificial kidney for acute dialysis in humans in 1943. His rotating drum kidney consisted of 30-40 meters of cellophane tubing in a stationary 100-litre tank [2]. Alwall then further modified and improved the original Kolff dialysis apparatus [3]. The development of the arteriovenous shunt by Quinton and sCribner in 1960 made maintenance dialysis of patients with chronic renal failure possible [4]. In 1977, Kramer described the first continuous form of dialysis specifically dedicated to critically ill patients: continuous arteriovenous hemofiltration (CAVH). In CAVH, blood flow in the circuit was driven by a spontaneous arteriovenous pressure gradient and spontaneous ultrafiltration (UF) occurred depending on the transmembrane pressure gradient (TMP). If needed, fluid losses were replaced by an equivoluminous saline solution [5]. CAVH was in the nineties gradually replaced by continuous venovenous replacement therapies, by use of a simple especially dedicated and developed CRRT machine. Further improvements in monitoring, membrane biocompatibility and dialyzer design were made during the past decades [1].

4.2.2. Principles of dialysis Dialysis literally means "to pass across". It consists of blood purification based on the physico-chemical process of allowing water and solute transport through a semipermeable membrane and then discarding the waste products. The separation mechanisms involved in renal replacement therapy are based on the principle of water and solute transport according to two fundamental principles: diffusion (solutes) and convection (water and solutes). During dialysis there are interactions between convection and diffusive modes of solute transport [6]. Hemodialysis (HD) is based on the diffusion principle. It is a passive process by which solute moves from an area of high concentration to an area of low concentration down a concentration gradient. During IHD and continuous venovenous hemodialysis (CVVHD) solutes cross the membrane driven by the concentration gradient between blood and dialysate. The solute flux (J) depends on the diffusion coefficient of the solute in the solvent (D_{AB}), the concentration gradient (ΔC) and the area (A) and thickness (ΔX) of the semipermeable membrane:

$$J = -D_{AB} * \Delta C * A / \Delta X$$

The negative sign indicates the direction of the solute flux towards the lower solute concentration.

In this process, the total volume of plasma water cleared from solute per unit of time (or "clearance") mainly depends upon the molecular weight of the solute, the properties of the membrane, and the dialyzer dialysate and blood flows. The diffusive nature of HD, and the high dialysate flow rates, makes it a highly effective "blood purification strategy", which allows intermittent therapy.

Hemofiltration (HF) is based upon convection during which solutes and water are transported across a semi-permeable membrane driven by the TMP. The process is called ultrafiltration UF. In other words, during hemofiltration plasma water is ultrafiltered across the membrane driven by the TMP and solutes are carried with it (solute drag). The UF rate depends on the TMP, which is typically adjusted by application of variable negative pressure at the dialysate side of the membrane, and the membrane's permeability to water (indicated by the UF coefficient K_{uf}).

During continuous venovenous hemofiltration (CVVH), the volume of the ultrafiltrate is continuously substituted by replacement fluid which can be delivered in ready-to-use bags. When the substitution fluid is administered downstream of the filter outlet, it is referred to as postdilution HF. When infused upstream of the filter, it is referred to as predilution HF. In general, convection contributes little to the clearance of rapidly diffusible small solutes such as urea, but can add significantly to the diffusive clearance of the larger middle molecules by high-flux membranes. During continuous venovenous hemodiafiltration (CVVHDF) both convection and diffusion are applied [7].

All forms of RRT rely on the above mentioned principles of diffusion and/or convection. Over the past years, various techniques for RRT, either intermittent or continuous, have become available for critically ill patients with AKI [8]. Classically, two major dialysis techniques are used in the ICU: conventional IHD and CRRT. More recently, hybrid therapies such as Slow Extended Daily Dialysis (SLEDD) combining aspects from both IHD and have found their way into the ICU [9].

IHD has been used in the ICU since the 1960s and was until the early 1980s the only treatment option for AKI in the ICU. IHD was first developed for chronic renal failure patients as a mainly diffusive but highly efficient therapy for toxin and fluid removal. It necessitates on-line dialysate production, a water-treatment module and a dialysis monitor. As its name suggests, IHD is applied on an intermittent base. In critically ill patients possible drawbacks of the intermittent nature are a "saw-tooth" pattern of metabolic control and the potential for hemodynamic intolerance resulting in difficulties to reach volume. This led to the development of CRRT which is a convective but low-efficiency therapy applied applied continuously using industrially prepared substitution fluids in bags. It was therefore proposed as an alternative to IHD in critically ill patients with sepsis, shock and multi-organ failure [10].

To counter these disadvantages "hybrid techniques" have been developed. SLEDD combines the advantages of CRRT and IHD by using a dialysis monitor and water-treatment module for on-line production of dialysate to perform slow, but extended and daily, HD [8].

4.2.3. Epidemiology of AKI treated with RRT in the ICU The Finnish Acute Kidney Injury (FINNAKI) trial reported an incidence of RRT in critically ill patients with AKI of 10.2% [11]. According to the recent multinational AKI-EPI study, AKI treated with RRT (AKI-RRT) occurs in 13.5% of ICU patients [12]. This rate is higher compared to previous studies that reported a population-based incidence of RRT utilization among critically ill patients with AKI of 11-19 cases per 100,000, representing 4-8% of all critically ill patients [13-15]. AKI-RRT is associated with adverse outcomes such as increased length-of-stay, short- and long-term mortality and end-stage kidney disease (ESKD).

4.3 CONTROVERSIAL ISSUES REGARDING RRT IN CRITICALLY ILL PATIENTS WITH ACUTE KIDNEY INJURY

Although RRT has been in use for more than half a century, many aspects of this therapy remain controversial. Whether or not to provide RRT, and when to initiate RRT are two fundamental issues in most cases of severe AKI [16]. In particular, no consensus has been reached on the timing of initiation and discontinuation of RRT, modality and intensity of RRT [17].

4.3.1. Indications and timing of initiation of renal replacement therapy in critically ill patients with acute kidney injury The concept of timing of RRT is based on two fundamental questions: i) whether or not to provide RRT and ii) when to initiate RRT. All aspects of current treatment of AKI are basically supportive. The primary goal of RRT is to compensate for the loss of renal function that characterizes AKI. In 2012 the KDIGO work group formulated practice guidelines concerning prevention and treatment of acute kidney injury [16]. The treatment of AKI with RRT has the following goals: i) to maintain fluid and electrolyte, acid-base, and solute homeostasis; ii) to prevent further insults to the kidney; iii) to permit renal recovery; and iv) to allow other supportive measures (e.g. nutrition support, antibiotics) to proceed without limitation or complications. Ideally, therapeutic interventions should be designed to achieve the above goals and a systematic assessment of all these factors is key to determine the optimal timing for initiation of dialysis. In addition, the concept of "primum non nocere" – do no harm – may overrule the obvious benefits of RRT.

At present there is no widely accepted definition of "timing of initiation" of RRT. Timing of initiation of RRT can be described by qualitative criteria e.g. time from hospital admission to RRT, or by a more quantitative characterization based on severity of illness or stages of kidney failure, e.g. absolute values of or serum urea or serum creatinine concentration or changes to the same versus a predefined baseline point.

Traditionally accepted indications for RRT are electrolyte disorders, progressive uremia, acid-base disorders, oligoanuria and fluid overload. Although also being considered indications to initiate RRT, uremic complications due to severe AKI are rarely seen in modern day ICU patients. In daily practice, the precise timing of RRT is usually a matter of clinical judgment and often based on clinical features of volume overload and biochemical parameters such as azotemia, hyperkalemia and severe acidosis [18]. In a survey by Ricci et al, 90 different criteria to initiate RRT are reported, with oligo-anuria the most frequently reported, in 27% [19]. More recently, Clark et al. found in a prospective study and in a survey, both conducted in Canada, that RRT was initiated early after hospital presentation and ICU admission. At initiation of RRT, patients already had advanced AKI, were severely ill and suffered from multiorgan failure [20]. Another non-renal indication for initiation of RRT in the ICU is AKI caused by drug overdose and intoxications. Severe sepsis and septic shock are associated with AKI in up to 50% of the ICU patients. Prophylactic dialysis in sepsis has been discussed in association with the hypothesis that it can possibly influence inflammatory mediator concentration. However, there is no evidence supporting the use of prophylactic RRT in sepsis [21].

Historically, timing of initiation of RRT was based on serum urea. The initial goal was to prevent the occurrence of overt uremic symptoms such as pericarditis, neuropathy or coma. This extent of uremia is no longer observed in the current setting of AKI in critically ill patients. However, at present the optimal threshold for serum urea to initiate RRT is still unknown. Landmark studies on this topic were performed 10 to 38 years ago and currently have limited value. Firstly, the individual studies were underpowered and included patients from very specific cohorts [22-26]. Secondly, the biological rationale that urea is a good biomarker for severity and duration of AKI is highly debatable. Serum urea is determined by many other variables that have no relation to kidney function, such as dehydration, catabolism, ARDS, gastrointestinal bleeding etcetera [27]. Finally, the association between serum urea as a cut-off biomarker for initiation of RRT and outcome is unclear. So despite being pointed out as a parameter for initiation of RRT according to the archetypal textbooks, AKIN and KDIGO guidelines, further research is needed to clarify the validity of serum urea as a biomarker for assessment of timing of initiation of RRT. Likewise the use of a sCr threshold as RRT initiation trigger is debatable. Clark et al. demonstrated that 64.0% of the patients had severe AKI (AKIN-3, based

on sCr concentrations) at initiation of RRT. This suggests that the impact of sCr in the decision whether or not to initiate RRT is rather limited [20]. These data are in line with the results of the BEST Kidney trial, in which almost half of the clinicians did not consider sCr concentrations as a trigger for initiation of RRT [13]. These findings should be taken into consideration when designing research protocols for future interventional studies on the optimal timing of initiation of RRT in critically ill patients with AKI [20].

Over the years, initiation of RRT has become more frequently guided by oliguria and volume overload. Fluid overload is a frequent complication of AKI. A sub-analysis of the Sepsis Occurrence in Acutely Ill Patients (SOAP) database showed that after correction for other covariates, a positive fluid balance was associated with an increased 60-day mortality in AKI patients (OR=1.21, 95% CI=1.19, 1.28) [28]. Others have confirmed the association between volume overload and mortality in AKI patients [29, 30]. It is uncertain whether volume overload serves as a surrogate marker for severity of illness or is a contributing factor in itself. Volume overload may therefore be an important parameter for the timing of initiation of RRT. Although diuretics are frequently administered in oliguric patients with AKI, their benefit has not been proven [16, 31].

Acid-base abnormalities are a frequent clinical problem in patients with severe AKI. In critically ill patients these acid-base disturbances frequently appear as metabolic acidosis with elevated lactate concentration. This possible life-threatening condition is associated with high mortality rates, making this an accepted indication for initiation of RRT [16]. Therefore, already since the 1960s, RRT has been used for the correction of acid-base disturbances as an adjunct to the treatment of the underlying cause [32]. In addition, where hemodynamic instability is observed, CRRT is often used to correct acidosis [33, 34]. Surprisingly, despite more than 50 years of practice with the use of RRT in AKI patients with severe lactic acidosis (SLA), evidence concerning dialysis for life-threatening SLA is lacking. The most recent study on this topic was published more than 15 years by Hilton et al [35]. They didn't report the incidence of lactic acidosis in critically ill patients with AKI but found that patients with SLA and AKI supported with bicarbonate buffered hemofiltration had a mortality of 71.5%. During the study period, mortality in AKI patients without lactic acidosis was 25.6%. The authors experienced a temporary physiological benefit in patients with lactic acidosis treated by bicarbonate buffered hemofiltration. A survival benefit could not be demonstrated in these patients. Due to a lack of evidence of outcome benefit, no standard criteria for initiating RRT in acidotic patients exist. On the one hand, metabolic acidosis associated with AKI can usually be corrected with bicarbonate and should rarely require urgent dialysis if not accompanied by oligo-anuria and volume overload or uremia [36]. On the other hand, it is widely accepted that patients with life threatening severe acidosis and AKI should be dialyzed emergently [16]. However, in the latter case, many clinicians hesitate to initiate RRT as it may be seen as futile because of the high mortality rates. Research should not only focus on the current epidemiology of SLA in critically ill patients with AKI-RRT, but should also assess possible determinants of outcome in this group of patients.

From a pathophysiological viewpoint it seems logical that timing should be defined on severity of AKI and associated organ failure rather than on a temporal definition. However, due to the conflicting literature and because of concern for the well-known risks associated with the RRT procedure, clinicians tend to disregard quantitative data and therefore delay RRT when they suspect that patients may recover. The decision-making on the initiation of RRT is further hampered by the fact that the application of RRT itself may compromise renal recovery. RRT-associated hemodynamic instability, vascular catheter-related bacteremia and sepsis and cytokine activation exposure to the extracorporeal circuit may delay recovery of renal function and increase the progression of CKD [37]. Whether these risks outweigh the potential benefits of early initiation of RRT is still unclear. Therefore, additional research to define the optimal timing of initiation of RRT is needed.

4.3.2. Modality of RRT Both CRRT and IHD may achieve a satisfactory degree of metabolic control in most patients. Ideally, IHD may be indicated for correction of acute metabolic or toxic derangements in hemodynamically stable patients. As such it also provides mobility of the patient and may be a more suitable option when patients are soon to leave the ICU. If needed, it can be performed without anticoagulation, which offers an extra advantage in patients at risk of bleeding. Although not supported by hard evidence, CRRT has been suggested to offer more hemodynamic stability and easier fluid management, better solute control and more stable intracranial pressure, compared with standard IHD [10]. Being a hybrid modality, SLEDD offers a convenient way to control electrolytes and fluid balance in combination with hemodynamic stability [8]. Despite these "theoretical" advantages, there is no evidence in favour for a specific RRT modality [17]. Peritoneal dialysis (PD) remains widespread, especially in low-income countries. A systematic review based on limited quality data on PD for AKI was set up by Chionh et al [38]. They found no differences in mortality between PD and extracorporeal blood purification in AKI, suggesting that PD may be a viable option.

4.3.3. Dialysis dose Strategies to improve outcome in critically AKI-RRT patients may include optimization of delivered RRT dose. However, this topic lies outside the scope of this work, and will therefore not be addressed in depth. In brief, the RENAL and ATN trial showed that increased intensity of RRT was not associated with improved patient or kidney outcomes [39, 40]. Also, a recent meta-analysis including these trials was similarly negative [41].

5. Studying outcomes and defining end-points of acute kidney injury treated with renal replacement therapy in critically ill patients

The above-mentioned controversies are not merely academic but may impact outcomes. Currently there is an emerging spectrum of outcome measures in ICU epidemiological studies. The term endpoint refers to an outcome to be measured in a classical clinical trial. These outcome measures can be categorized as clinical endpoints, surrogate endpoints and composite endpoints [42].

5.1 CLINICAL ENDPOINTS

A clinical endpoint is an aspect of a patient's clinical or health status that can be measured. It is, as it suggests, clinically relevant and is both accepted and used by physicians and patients. Clinical endpoints may be a clinical event (such as mortality), a measure of clinical status (e.g. dialysis dependency (DD)) or health related quality of life (HrQOL). Endpoints such as mortality are considered hard endpoints, in contrast with "soft" endpoints like patient reported outcomes (PRO), e.g. HrQOL [43].

5.1.1. Mortality Mortality as an endpoint measure can be reported as a dichotomous outcome measure and is as such a clear and easy to handle endpoint. This is an advantage over endpoints like renal recovery which require measuring whether the kidney function is increasing or decreasing. The success of intensive care medicine has traditionally been gauged by the proportion of patients alive at hospital/ICU discharge or at day 28. However, these endpoints may underestimate the true burden of disease, including kidney disease. In modern-day ICU care, we should aim for more relevant endpoints such as long-term mortality (90 days, 6 months, one-year).

Initially, studies focused on long-term mortality were mostly performed in patients with "AKI defined by treatment with RRT". The RENAL study reported a 44.7% mortality rate three months after initiation of RRT [39]. Bagshaw and co-workers described a 1-year mortality of 63.8% in a population-based study [14]. Korkeila reported 65% mortality at 5 years in a mixed Finnish ICU population with AKI without pre-existing renal failure [44]. Ahlström confirmed these findings in a cross-sectional cohort study on patients from a mixed ICU and dialysis unit with a 5 years mortality of 70% [45].

However, assessing long-term mortality based on "AKI defined by RIFLE criteria" highlights the stepwise adverse long-term mortality associated with different stages of AKI. This has been confirmed by several more recent studies in which the modern RIFLE, AKIN and KDIGO definitions for AKI were used. For instance, recently, Fuchs and co-workers described the strong relationship between AKI and mortality in a large retrospective study including more than 15,000 ICU patients with no history of end stage kidney disease (ESKD). Patients with AKIN 3 had 61% higher mortality risk 2 years after ICU discharge compared with patients without AKI [46]. Finally, Coca et al demonstrated in a systematic review and meta-analysis of 49 studies that even mild increases in serum creatinine were associated with adverse short and long-term outcomes [47]. More recently, Linder et al demonstrated in a prospective cohort study of more than 2,000 critically ill patients with AKI an adjusted 10-year mortality risk of 1.26. Even stage 1 AKI was associated with 10-year decreased survival [48].

5.1.2. Patient associated morbidity endpoints

Renal recovery

Until recently, it was widely accepted that most patients surviving AKI fully recovered renal function. From a pragmatic perspective renal recovery was usually defined as the absence of dialysis. Due to the recent standard definitions of AKI, it has become clear that AKI survivors may develop CKD and that some will progress to ESRD [16,49]. To this date no uniform definition for renal recovery exists. This lack of standard definition explains the wide variation in renal recovery rates reported in literature ranging from 1 to 40% [50]. Definitions of renal recovery are often based on sCr. A major weakness in this respect is the frequent absence of a standard or "baseline" sCr. Ideally, this baseline sCr should be measured in the 3-12 months prior to the event. Several approaches (e.g. the MDRD backcalculation of sCr) have been used to determine a reference value of sCr, but they are subject to discussion [51]. An additional problem with this definition is the poor sensitivity of sCr. A loss of more than half of the nephrons is needed to alter sCr concentrations. Ideally, the definition of renal recovery should quantify lost preexisting kidney function, as well as current residual kidney function and reserve, identify when recovery is complete and provide information related to outcome. Very recently, the ADQI 16 Work group proposed an operational definition of renal recovery as a reduction in peak AKI stage (based on KDIGO criteria) further refined by change in sCr level, GFR, biomarkers of injury or repair and/or return of renal reserve [52]. The epidemiological data on renal recovery are very heterogenous depending on the study cohort, the definition used and the timing of assessment. Chertow et al demonstrated that 33% of patients surviving AKI treated with RRT were still on RRT after one year [53]. Schiffl et al reported that maximal improvement or normalization of renal function took place within the first year [54]. Bagshaw et al evaluated renal recovery in critically ill patients, including 45% with preexisting CKD. At hospital discharge, 32% of the patients was dialysis dependent [55].The link between AKI, CKD and ESKD was demonstrated in a large population study by Ali et al. They reported an incidence of ESKD after 90 days of 0.6% in AKI patients without preexisting CKD versus 6.0% in patients with previous renal dysfunctioning [56]. Further, patients suffering from an episode of acute-on-chronic kidney disease have an increased risk of progression towards ESKD [57]. Given the fact that CKD stage is associated with a proportionally higher risk of developing

new episodes of AKI [53], these patients may eventually be trapped in a downward spiral as their renal functional reserve progressively reduces [58]. Interestingly, the progression to CKD is determined by the frequency of AKI episodes and the severity of the AKI [59]. Aside from preexisting CKD, advanced age could be identified as major risk factor for incomplete renal recovery [60]. Other well-defined risks for poor renal recovery are the presence of diabetes, congestive heart failure, hypertension, proteinuria but also the general comorbidity status of the patient, expressed by the Charlson Comorbidity Index score [61,62]. Whether RRT modality influences renal outcome after an AKI-RRT episode remains controversial.

A meta-analysis by Schneider et al analyzed data on dialysis dependency among critically ill patients who survived an AKI-RRT episode. They found that initial support with IRRT might be associated with a higher rate of dialysis dependency. However, this finding was largely based on data from observational trials and therefore prone to bias [63]. Given the fact that renal recovery implies more than absence of dialysis, some investigators suggest that hospital survivors of severe AKI should be followed by a nephrologist or an "AKI Follow-Up Clinic" after hospital discharge to prevent that CKD remains undiagnosed in these patients [64].

Health related Quality of Life

There has been a historic emphasis on mortality outcomes after critical illness. Naturally, mortality is considered a decisive endpoint, but it may distract the attention from the reality of the post-ICU experience with long-term physical and physiological dysfunctioning. The notion that mortality beyond hospital discharge is not the only relevant clinical endpoint has led to an increasing interest in HrQOL in patients surviving ICU. HrQOL measures the impact of disease and treatment on the lives of patients and is defined as *"the capacity to perform the usual daily activities for a person's age and major social role"* [60]. HrQOL is a multidomain concept including physical functioning, psychological well-being, and social role functioning. It is an example of a PRO which is based on data provided by patients or by people who can report on their behalf (proxies). The Food and Drug Administration (FDA) nicely defines a PRO as *"a measurement based on reports that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else"* [66]. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response [43].

Health-related quality of life is determined by i) the side effects of treatment, and ii) symptoms of the disease. A treatment with RRT is likely to improve HrQOL by preventing AKI associated symptoms. On the contrary, the side effects of RRT obviously affect the HrQOL of the patient, making this a much nebulous endpoint than for example mortality [62]. HrQOL is classically measured using a brief questionnaire in which patients rate their ability to function in various ways. Patients typically fill out the questionnaire several times during the course of the trial. Studies describing HrQOL in patients recovering from AKI commonly use the Short Form-36 (SF-36), the Nottingham Health Profile (NHP) and the European Quality of Life score (EQ-5D) [68].

Unfortunately, data on long-term HrQOL in ICU patients with AKI-RRT are scarce. Oeyen et al presented a detailed systematic review of the literature concerning HrQOL after ICU discharge [69]. HrQOL is affected in critically ill patients suffering from conditions frequently associated with AKI-RRT such as acute respiratory distress syndrome severe ARDS, severe sepsis and major trauma, all conditions associated with AKI. Data regarding HrQOL in AKI-RRT show that these patients have decreased HrQOL compared to the general population but perceie HrQOL as good [45,70]. As Oeyen et al demonstrated, most studies investigating HrQOL have many drawbacks [69]. Their design is often retrospective [44, 71-73], they are characterized by short-term HrQOL evaluation [15, 44, 45, 70, 71, 73-76], lack baseline HrQOL assessment [44, 45, 71, 72, 75, 78] or are outdated [44, 71, 72, 74, 78]. A significant

proportion of critically ill patients with AKI treated with RRT will develop ESKD. DD is not only associated with substantial health care costs, but is likely to affect HrQOL. It is therefore of great interest to assess HrQOL in this specific group of patients.

5.2 SURROGATE ENDPOINTS

A surrogate or intermediate endpoint is an endpoint that is intended to replace a clinical endpoint of interest that cannot be observed. A surrogate endpoint may be a biomarker (e.g. serum urea or lactate concentration) that is intended as substitute for a clinical endpoint. A surrogate endpoint usually tracks the progress or extent of the disease. Investigators choose a surrogate endpoint when the definite endpoint is inaccessible due to cost, time or difficulty of measurement [43]. The problem with a surrogate endpoint is its validity as it may provide an incomplete picture of the clinical endpoint it reflects. Therefore, choice of the surrogate endpoint should be approached with caution, since these measures may be crude or relatively reflective surrogates for the primary endpoint [79]. Piantadosi gives the following characteristics of a useful surrogate endpoint: i) it can be measured simply and without invasive procedures ii) it is related to the causal pathway for the definite endpoint iii) it yields the same statistical interference as the definite endpoint iv) it should be responsive to the effects of treatment [80]. Even a validated biomarker may have substantial variability in both its physiological expression and its association with the clinical outcomes of interest which may adversely affect the study and can lead to misleading results.

5.3 COMPOSITE ENDPOINTS

A composite or aggregated endpoint combines two or more single events. Patients who have experienced any of the components of a composite endpoint are considered to have experienced the composite endpoint. This concept has been adopted from cardiovascular literature, where composite endpoints as Major Adverse Cardiac Events (MACE) are widely used [81]. A composite endpoint is often used when it makes clinical sense to group them. Further, the composite endpoint will occur more frequently than any of the individual components. So this is particularly interesting when the individual events included in the score are rare. They usually refer to combined morbidity and mortality endpoints [82]. The 2011 Workshop of the National Institute of Diabetes and Digestive and Kidney Diseases on Clinical Trial Design presented a kidney composite endpoint of death, dialysis administration and incomplete renal recovery for AKI [83]. More recently this renal composite endpoint – Major Adverse Kidney Events (MAKE) – was further operationalized including death, dialysis, or worsened renal function, which was defined as a 25% or greater decline in estimated glomerular filtration rate (eGFR) [84,85].

Ideally, these “pooled” endpoints have a higher incidence than each of their components, reducing required sample size and increasing statistical efficiency [86]. In addition, by combining these outputs into a single outcome measure, competing risk between the individual components is avoided. However, pooled endpoints such as MAKE have to be well defined and meticulously constructed. The unclear definition of renal recovery as one of the components of MAKE may hamper correct interpretation. Furthermore, the use of composite endpoints in clinical trials can easily be biased as component endpoints may be selected to ensure statistical significance [82]. Future research evaluating these “newer” endpoints in the field of AKI is imperative.

REFERENCES

[1] Gottschalk CW, Fellner SK: History of the science of dialysis. Am J Nephrol 1997, 17(3-4):289-298.

[2] Kolff WJ: First Clinical Experience with the Artifical Kidney. Ann Intern Med 1965, 62:608-619.

[3] Alwall N, Norvitt L, Steins AM: On the artificial kidney; some experiences during the study of dialytic treatment on animals with uremia caused by mercuric chloride poisoning. Acta Med Scand 1949, 132(5):477-486.

[4] Quinton W, Dillard D, sCribner BH: Cannulation of blood vessels for prolonged hemodialysis. Trans Am Soc Artif Intern Organs 1960, 6:104-113.

[5] Kramer P, Wigger W, Rieger J, Matthaei D, Scheler F: [Arteriovenous haemofiltration: a new and simple method for treatment of over-hydrated patients resistant to diuretics]. Klin Wochenschr 1977, 55(22):1121-1122.

[6] Ricci Z, Romagnoli S, Ronco C: Renal Replacement Therapy. F1000Res 2016, 5.

[7] Uehlinger DE, Jakob SM, Ferrari P, Eichelberger M, Huynh-Do U, Marti HP, Mohaupt MG, Vogt B, Rothen HU, Regli B et al: Comparison of continuous and intermittent renal replacement therapy for acute renal failure. Nephrol Dial Transplant 2005, 20(8):1630-1637.

[8] Lameire N, Van Biesen W, Vanholder R: Dialysing the patient with acute renal failure in the ICU: the emperor's clothes? Nephrol Dial Transplant 1999, 14(11):2570-2573.

[9] Villa G, Neri M, Bellomo R, Cerda J, De Gaudio AR, De Rosa S, Garzotto F, Honore PM, Kellum J, Lorenzin A et al: Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. Crit Care 2016, 20(1):283.

[10] Friedrich JO, Wald R, Bagshaw SM, Burns KEA, Adhikari NKJ: Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. Crit Care 2012, 16:R146

[11] Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, Haapio M, Inkinen O, Parviainen I, Suojaranta-Ylinen R et al: Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 2013, 39(3):420-428.

[12] Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D et al: Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015, 41(8):1411-1423.

[13] Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E et al: Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005, 294(7):813-818.

[14] Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, Godinez-Luna T, Svenson LW, Rosenal T: Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 2005, 9(6):R700-709.

[15] Vaara ST, Pettilä V, Reinikainen M, Kaukonen KM, Consortium FIC: Population-based incidence, mortality and quality of life in critically ill patients treated with renal replacement therapy: a nationwide retrospective cohort study in Finnish intensive care units. Crit Care 2012, 16(1):R13.

[16] KDIGO AKI Work Group. KDIGO clinical practice guideline for cute kidney injury Kidney Int Suppl 2012, 2:1-138.

[17] Kellum JA, Ronco C, Vincent JL: Unveiling current controversies in acute kidney injury. Contrib Nephrol 2011, 174:1-3.

[18] Macedo E, Mehta RL: Timing of dialysis initiation in acute kidney injury and acute-on-chronic renal failure. Semin Dial 2013, 26(6):675-81

[19] Ricci Z, Ronco C, D'Amico G, De Felice R, Rossi S, Bolgan I, Bonello M, Zamperetti N, Petras D, Salvatori G et al: Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. Nephrol Dial Transplant 2006, 21(3):690-696.

[20] Clark E, Wald R, Levin A, Bouchard J, Adhikari NK, Hladunewich M, Richardson RM, James MT, Walsh MW, House AA et al: Timing the initiation of renal replacement therapy for acute kidney injury in Canadian intensive care units: a multicentre observational study. Can J Anaesth 2012, 59(9):861-870.

[21] Ronco C, Inguaggiato P, D'Intini V, Cole L, Bellomo R, Poulin S, Bordoni V, Crepaldi C, Gastaldon F, Brendolan A et al: The role of extracorporeal therapies in sepsis. J Nephrol 2003, 16 Suppl 7:S34-41.

[22] Parsons FM, Hobson SM, Blagg CR, Mccracken BH: Optimum time for dialysis in acute reversible renal failure. Description and value of an improved dialyser with large surface area. Lancet 1961, 1(7169):129-134.

[23] Fischer RP, Griffen WO, Reiser M, Clark DS: Early dialysis in the treatment of acute renal failure. Surg Gynecol Obstet 1966, 123(5):1019-1023.

[24] Kleinknecht D, Jungers P, Chanard J, Barbanel C, Ganeval D: Uremic and non-uremic complications in acute renal failure: Evaluation of early and frequent dialysis on prognosis. Kidney Int 1972, 1(3):190-196.

[25] Conger JD: A controlled evaluation of prophylactic dialysis in post-traumatic acute renal failure. J Trauma 1975, 15(12):1056-1063.

[26] Gillum DM, Dixon BS, Yanover MJ, Kelleher SP, Shapiro MD, Benedetti RG, Dillingham MA, Paller MS, Goldberg JP, Tomford RC: The role of intensive dialysis in acute renal failure. Clin Nephrol 1986, 25(5):249-255.

[27] Waikar SS, Bonventre JV: Can we rely on blood urea nitrogen as a biomarker to determine when to initiate dialysis? Clin J Am Soc Nephrol 2006, 1(5):903-904.

[28] Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL, Investigators SOiAIPS: A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008, 12(3):R74.

[29] Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL, Group PtICiARDPS: Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009, 76(4):422-427.

[30] Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, Laurila JJ, Mildh L, Reinikainen M, Lund V et al: Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012, 16(5):R197.

[31] Joannidis M, Druml W, Forni LG, Groeneveld AB, Honore P, Oudemans-van Straaten HM, Ronco C, Schetz MR, Woittiez AJ, Medicine CCNWGotESoIC: Prevention of acute kidney injury and protection of renal function in the intensive care unit. Expert opinion of the Working Group for Nephrology, ESICM. Intensive Care Med 2010, 36(3):392-411.

[32] Naka T, Bellomo R: Bench-to-bedside review: treating acid-base abnormalities in the intensive care unit--the role of renal replacement therapy. Crit Care 2004, 8(2):108-114.

[33] Colombi A, Thölen H: Haemodialysis in the treatment of lactic acidosis associated with acute hepatic and renal failure. Postgrad Med J 1971, 47(551):628-631.

[34] Bellomo R, Lipcsey M, Calzavacca P, Haase M, Haase-Fielitz A, Licari E, Tee A, Cole L, Cass A, Finfer S et al: Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis. Intensive Care Med 2013, 39(3):429-436.

[35] Hilton PJ, Taylor J, Forni LG, Treacher DF: Bicarbonate-based haemofiltration in the management of acute renal failure with lactic acidosis. QJM 1998, 91(4):279-283.

[36] Gauthier PM, Szerlip HM: Metabolic acidosis in the intensive care unit. Crit Care Clin 2002, 18(2):289-308, vi.

[37] Palevsky PM, Baldwin I, Davenport A, Goldstein S, Paganini E: Renal replacement therapy and the kidney: minimizing the impact of renal replacement therapy on recovery of acute renal failure. Curr Opin Crit Care 2005, 11(6):548-554.

[38] Chionh CY, Soni SS, Finkelstein FO, Ronco C, Cruz DN: Use of peritoneal dialysis in AKI: a systematic review. Clin J Am Soc Nephrol 2013, 8(10):1649-1660.

[39] Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R et al: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009, 361(17):1627-1638.

[40] Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM et al: Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008, 359(1):7-20.

[41] Van Wert R, Friedrich JO, Scales DC, Wald R, Adhikari NK, Group UoTAKIR: High-dose renal replacement therapy for acute kidney injury: Systematic review and meta-analysis. Crit Care Med 2010, 38(5):1360-1369.

[42] Ar W: Conducting clinical trials. A theoretical and practical guide. In.; 2008.

[43] Ording AG, Cronin-Fenton D, Ehrenstein V, Lash TL, Acquavella J, Rørth M, Sørensen HT: Challenges in translating endpoints from trials to observational cohort studies in oncology. Clin Epidemiol 2016, 8:195-200.

[44] Korkeila M, Ruokonen E, Takala J: Costs of care, long-term prognosis and quality of life in patients requiring renal replacement therapy during intensive care. Intensive Care Med 2000, 26(12):1824-1831.

[45. Ahlström A, Tallgren M, Peltonen S, Räsänen P, Pettilä V: Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Med 2005, 31(9):1222-1228.

[46] Fuchs L, Lee J, Novack V, Baumfeld Y, Scott D, Celi L, Mandelbaum T, Howell M, Talmor D: Severity of acute kidney injury and two-year outcomes in critically ill patients. Chest 2013, 144(3):866-875.

[47] Coca SG, Singanamala S, Parikh CR: Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012, 81(5):442-448.

[48] Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH: Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. Am J Respir Crit Care Med 2014, 189(9):1075-1081.

[49] Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011;79:1361-1369

[50] Macedo E, Mehta RL. Renal recovery after acute kidney injury. Contrib Nephrol. Basel, Karger 2016;187:24-35

[51] Siew ED, Ikizler TA, Matheny ME, Shi Y, Schildcrout JS, Danciu L,et al. Estimating baseline kidney function in hospitalized patients with impaired kidney function. Clin J Am Soc Nephrol 2012;7:712-719

[52] Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol 2017

[53] Chertow GM, Christiansen CL, Cleary PD, Munro C, Lazarus JM: Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. Arch Intern Med 1995, 155(14):1505-1511.

[554] Schiffl H, Fischer R: Five-year outcomes of severe acute kidney injury requiring renal replacement therapy. Nephrol Dial Transplant 2008, 23(7):2235-2241.

[55] Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Muckenski M, et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 2005, 9:R700-709

[56] Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 2007, 18:1292-1298

[57] Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE: Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int 2009, 76(10):1089-1097.

[58] Singbartl K, Kellum JA: AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int 2012, 81(9):819-825.

[59] Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE: The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011, 79(12):1361-1369.

[60] Srisawat N, Wen X, Lee M, Kong L, Elder M, Carter M, et al. Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol 2011, 6:1815-1823

[61] Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol 2009, 4:891-898

[62] Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic disease following reversible acute kidney injury. Kidney Int 2012, 81:477-485

[63] Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, Cass A, Gallagher M: Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med 2013, 39(6):987-997.

[64] Silver SA, Harel Z, Harvey A, Adhikari NK, Slack A, Acedillo R, Jain AK, Richardson RM, Chan CT, Chertow GM et al: Improving Care after Acute Kidney Injury: A Prospective Time Series Study. Nephron 2015, 131(1):43-50.

[65] Guyatt GH, Feeny DH, Patrick DL: Measuring health-related quality of life. Ann Intern Med 1993, 118(8):622-629.

[66] McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD: Interpreting patient-reported outcome results: US FDA guidance and emerging methods. Expert Rev Pharmacoecon Outcomes Res 2011, 11(2):163-169.

[67] Felce D, Perry J: Quality of life: its definition and measurement. Res Dev Disabil 1995, 16(1):51-74.

[68] Brazier J, Jones N, Kind P: Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire. Qual Life Res 1993, 2(3):169-180.

[69] Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM: Quality of life after intensive care: a systematic review of the literature. Crit Care Med 2010, 38(12):2386-2400.

[70] Delannoy B, Floccard B, Thiolliere F, Kaaki M, Badet M, Rosselli S, Ber CE, Saez A, Flandreau G, Guérin C: Six-month outcome in acute kidney injury requiring renal replacement therapy in the ICU: a multicentre prospective study. Intensive Care Med 2009, 35(11):1907-1915.

[71] Morgera S, Kraft AK, Siebert G, Luft FC, Neumayer HH: Long-term outcomes in acute renal failure patients treated with continuous renal replacement therapies. Am J Kidney Dis 2002, 40(2):275-279.

[72] Gopal I, Bhonagiri S, Ronco C, Bellomo R: Out of hospital outcome and quality of life in survivors of combined acute multiple organ and renal failure treated with continuous venovenous hemofiltration/ hemodiafiltration. Intensive Care Med 1997, 23(7):766-772.

[73] Abelha FJ, Botelho M, Fernandes V, Barros H: Outcome and quality of life of patients with acute kidney injury after major surgery. Nefrologia 2009, 29(5):404-414.

[74] Maynard SE, Whittle J, Chelluri L, Arnold R: Quality of life and dialysis decisions in critically ill patients with acute renal failure. Intensive Care Med 2003, 29(9):1589-1593.

[75] Morsch C, Thomé FS, Balbinotto A, Guimarães JF, Barros EG: Health-related quality of life and dialysis dependence in critically ill patient survivors of acute kidney injury. Ren Fail 2011, 33(10):949-956.

[76] Hofhuis JG, van Stel HF, Schrijvers AJ, Rommes JH, Spronk PE: The effect of acute kidney injury on long-term health-related quality of life: a prospective follow-up study. Crit Care 2013, 17(1):R17.

[77] Noble JS, Simpson K, Allison ME: Long-term quality of life and hospital mortality in patients treated with intermittent or continuous hemodialysis for acute renal and respiratory failure. Ren Fail 2006, 28(4):323-330.

[78] Hamel MB, Phillips RS, Davis RB, Desbiens N, Connors AF, Teno JM, Wenger N, Lynn J, Wu AW, Fulkerson W et al: Outcomes and cost-effectiveness of initiating dialysis and continuing aggressive care in seriously ill hospitalized adults. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Ann Intern Med 1997, 127(3):195-202.

[79] Fleming TR, Powers JH: Biomarkers and surrogate endpoints in clinical trials. Stat Med 2012, 31(25):2973-2984.

[80] Piantadosi S: Proper interpretation and analysis of censored events and studies that contain them. Mult Scler 2005, 11(6):624-625.

[81] Hermans WR, Foley DP, Rensing BJ, Rutsch W, Heyndrickx GR, Danchin N, Mast G, Hanet C, Lablanche JM, Rafflenbeul W: Usefulness of quantitative and qualitative angiographic lesion morphology, and clinical characteristics in predicting major adverse cardiac events during and after native coronary balloon angioplasty. CARPORT and MERCATOR Study Groups. Am J Cardiol 1993, 72(1):14-20.

[82] Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC: Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ 2010, 341:c3920.

[83] Palevsky PM, Molitoris BA, Okusa MD, Levin A, Waikar SS, Wald R, Chertow GM, Murray PT, Parikh CR, Shaw AD et al: Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. Clin J Am Soc Nephrol 2012, 7(5):844-850.

[84] Billings FT, Shaw AD: Clinical trial endpoints in acute kidney injury. Nephron Clin Pract 2014, 127(1-4):89-93.

[85] Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS et al: Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013, 17(1):R25.

[86] Freemantle N, Calvert M: Composite and surrogate outcomes in randomised controlled trials. BMJ 2007, 334(7597):756-757.

2

1. Objectives

1.1 OBJECTIVE 1

To describe the epidemiology of AKI treated with RRT in critically ill patients.

1.2 OBJECTIVE 2

To explore timing of initiation of RRT in the light of patient outcome by investigating some “classical” indications of RRT in critically ill patients.

1.3 OBJECTIVE 3

To assess the short- and long-term patient and kidney outcome in ICU patients with AKI treated with RRT. In addition, the recently proposed composite endpoint MAKE was studied.

1.4 OBJECTIVE 4

To evaluate the quality of life in ICU patients with AKI treated with RRT. This topic will be addressed in Study IV.

To address these objectives four studies were performed. **Study I** evaluates whether conventional serum urea cut-off values as described in the literature were associated with outcome at time of initiation of RRT for AKI. It explores the impact of timing of initiation of RRT in the light of patient outcome. **Study II** explores the epidemiology of severe lactic acidosis in critically ill patients with AKI treated with RRT. Factors that may influence outcome in these patients were evaluated. **Study III** describes the long-term patient and kidney outcomes in critically ill patients with AKI-RRT and evaluates possible modifying factors of outcome such as CKD, timing of initiation of RRT and RRT modality. **Study IV** assesses the long-term outcomes and quality-of-life of critically ill AKI-RRT patients at baseline, and at 3 months, 1 year and 4 years after ICU discharge and comparing quality of life with a cohort of matched non-AKI-RRT patients.

2. Methodology

2.1 DESIGN OF THE STUDIES

This doctoral thesis comprised 4 single center cohort analysis studies of critically ill patients with AKI-RRT at a tertiary care hospital. The Ghent University Hospital ICU consists of a 22-bed surgical ICU, a 14-bed medical ICU, an 8-bed cardiac surgery ICU and a 6-bed burn ICU. Study I and II had a retrospective design, study III and IV were prospective observational studies **(Table 1)**.

2.2 STUDY COHORT

The inclusion criteria were ICU patients aged ≥15 years who had AKI and were treated with RRT and who had follow-up data after hospital discharge. During the study period, an electronic patient data management system (PDMS) was gradually introduced. Only patients who were registered in the PDMS were included in the study. Exclusion criteria were extracorporeal blood purification techniques for reasons other than AKI, patients with CKD receiving chronic RRT, RRT initiated before admission to the ICU, and RRT immediately after kidney transplant. In the cases where a patient had several ICU episodes of AKI-RRT during the same hospital admission, we considered only the first episode. Indications for RRT, as well as the modality chosen (IHD, duration 2–4 h per treatment session; SLEDD, duration 6–12 h per treatment session; or CRRT (continuous venovenous hemofiltration or hemodialysis), were determined by

consensus between the attending intensivists and nephrologists and based on the clinical status of the patient (hemodynamic stability, fluid balance, respiratory status, acid-base balance). Continuous modalities are preferentially used in patients with severe shock, patients who are at risk for cerebral edema (e.g., liver cirrhosis), or patients for whom intensive and consistent fluid removal is pursued.

2.3. DATA COLLECTION

Data were recorded during the hospital stay. Baseline demographic parameters were retrieved from the hospital's electronic database and the ICU's electronic PDMS. Data on comorbidity and diagnostic categories were retrieved from the hospital administration's International Classification of Diseases, Ninth Revision (ICD-9), electronic coding system. Data on long-term follow-up were gathered from the patients' electronic medical records (e.g., during follow-up consultation or, in cases of absence of such a consultation, by contacting the primary care physician of the patient by e-mail or telephone).

Table 1.

Original studies included in the thesis: design, patient cohort and outcome measures.

STUDY I	STUDY II	STUDY III	STUDY IV
STUDY DESIGN			
Single Center Cohort Retrospective	Single Center Cohort Retrospective	Single Center Cohort Prospective	Single Center Matched Cohort Prospective
INCLUSION PERIOD			
2004-2007	2004-2007	2004-2012	2008-2012
STUDY COHORT			
AKI-RRT N= 302	AKI-RRT N= 342	AKI-RRT N= 959	AKI-RRT N= 121
FOLLOW-UP PERIOD			
hospital stay	24 hours	up to 8 years	4 years
CLINICAL ENDPOINTS			
MORTALITY			
hospital mortality	ICU mortality	icu mortality hospital mortality long-term mortality	long-term mortality
PATIENT ASSOCIATED MORBIDITY ENDPOINT			
		renal recovery dialysis dependency	long-term mortality
SURROGATE ENDPOINTS			
serum urea	lactate	serum creatinine GFR	SF-36 EuroQOL-5D
COMPOSITE ENDPOINTS			
		MAKE	

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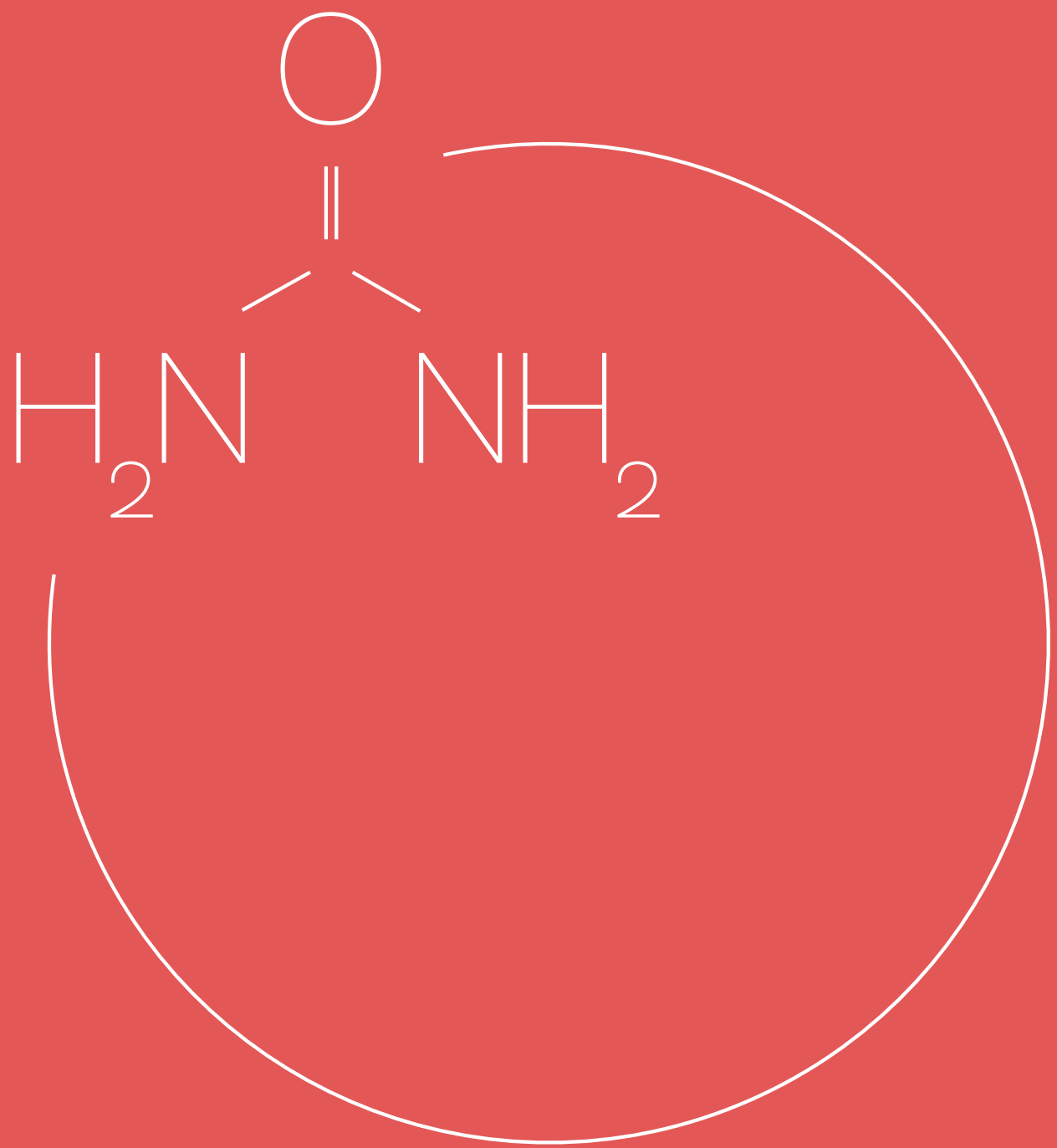
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3

Serum urea concentration is probably not related to outcome in ICU patients with acute kidney injury and renal replacement therapy

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PUBLISHED IN
Nephrol Dial Transplant. 2011 Oct;26(10):3211-8.

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BACKGROUND

AKI is a common complication in patients admitted to the intensive care unit (ICU). Among other variables, serum urea concentrations are recommended for timing of initiation of RRT. The aim of this study was to evaluate whether serum urea concentration or different serum urea concentration cut-offs as recommended in literature were associated with in-hospital mortality at time of initiation of RRT for AKI.

METHODS

This is a retrospective, single-centre study during a 3-year period (2004-2007), in a 44-bed tertiary care centre ICU on adult AKI patients who were treated with RRT.

RESULTS

Three hundred and two patients were included: 68.9% male, median age 65 y and APACHE II score of 21. The overall in-hospital mortality was 57.9%. Non-survivors were older (67 vs. 64 y, P=0.016), and had a higher APACHE II score (22 vs. 20, P<0.001). At time of initiation of RRT, they were more severely ill and had a lower serum urea concentration compared to survivors (130 vs.141 mg/dL, p=0.038). Serum urea concentration, as well as the different historical serum urea concentration cut-offs had low area under the curves for the receiver operating characteristic curve for prediction of mortality. In multivariate analysis, age, and at time of initiation of RRT, potassium, SOFA score with exclusion of points for AKI, and RIFLE class were associated with mortality, but serum urea concentration and the different cut-offs were not.

CONCLUSION

This retrospective study suggests that serum urea concentration and serum urea concentration cut-offs at time of initiation of RRT have no predictive value for in-hospital mortality in ICU patients with AKI.

1. Introduction

AKI treated with (RRT occurs in approximately 5% of ICU patients and has an incidence of approximately 200 - 300 patients per million inhabitants, comparable to the incidence of acute lung injury and acute respiratory distress syndrome [1-7]. It is associated with worse outcomes, such as increased length of stay, end-stage renal disease, cost and short- and long-term mortality [2,3]. Despite over five decades of experience with RRT for AKI, there is still no firm evidence on the criteria for initiation of RRT. According to an expert working group of the Acute Kidney Injury Network (AKIN), who summarized the available evidence, absolute indications for initiation of RRT include a serum urea concentration greater than 224 mg/dL (BUN>100 mg/dL), hyperkalaemia (>6 mmol/L and ECG abnormalities), hypermagnesaemia (>8 mEq/L), severe acidosis (pH<7.15), lactic acidosis related to methformin use, and anuria with diuretic resistant volume overload. In patients with AKI who do not fulfil absolute indications, serum urea concentration greater than 170 mg/dL (BUN>76 mg/dL) is considered a relative indication for initiation of RRT [8]. Serum urea concentrations have been used for timing of initiation of RRT since the early days of treatment of AKI patients. Since the 1960s, there is a trend to initiate RRT at lower serum urea concentrations (Table 1). One recent and several older studies found that a lower serum urea concentration at initiation of RRT was associated with better outcome [9-15]. Only 3 prospective intervention studies have evaluated this issue. None of these could demonstrate that initiation at lower serum urea concentration had an impact on outcome.

In view of the contradictions reported in literature we aimed to assess the relationship between serum urea concentration at time of initiation of RRT and in-hospital mortality.

⟶ KEY MESSAGE

The actually recommended serum urea concentration cut-offs at time of initiation of RRT have no predictive value for in-hospital mortality in critically ill patients with AKI.

2. Subjects and methods

This is a retrospective analysis of prospectively collected data to study the effect of serum urea concentration at initiation of RRT on in-hospital mortality.

2.1 STUDY POPULATION

We analyzed all ICU patients, age 15 year and older who had AKI and were treated with RRT during the period 2004-2007 at the Ghent University Hospital ICU and who were included in the electronic ICU PDMS. The ICU includes a 22 bed Surgical, a 14 bed Medical, a 6 bed Burn, and an 8 bed Cardiac Surgery ICU. Patients admitted at the Burn ICU were excluded from analysis because serum urea concentration in this cohort may be disproportionally increased compared to other types of ICU patients. Other exclusion criteria were extracorporeal blood purification techniques for other reasons than AKI, patients on chronic RRT, RRT initiated before admission to the ICU, and RRT immediately post kidney transplant. Treatment episodes with peritoneal dialysis, a modality incidentally used in our ICU, were also not considered. Indications for RRT, as well as the modality chosen [i.e. intermittent (duration 2 to 4 h per treatment session) or continuous hemodialysis (IHD/CHD), CVVH, or SLEDD (duration 6 to 12 h per treatment session)], were determined in consensus between the attending intensivists and nephrologists [19].

2.2 DATA COLLECTION

Demographic data were retrieved from the electronic hospital database, laboratory data from the laboratory database and patient data from the electronic ICU PDMS. Data were prospectively recorded at time of ICU admission and at time of initiation of RRT. For every parameter, the most abnormal value per day was registered. Serum concentrations of urea, creatinine, sodium and potassium were collected on admission at ICU, and at the start of RRT. Serum creatinine was collected at time of hospital admission. SAPS II (Simplified Acute Physiology Score) and APACHE II (Acute Physiologic Assessment and Chronic Health evaluation) scores were calculated on data collected during the first day of admission [20,21]. At time of initiation of RRT we calculated the SOFA score (Sequential Organ Failure Assessment) [22], and a SOFA score with omission of points for kidney insufficiency ($SOFA_{non\text{-}renal}$) [23]. Severity of AKI was also assessed at time of initiation of RRT by the RIFLE classification subdividing AKI into three categories of severity (Risk, Injury and Failure) and two categories of clinical outcome. RIFLE severity class was assessed on serum creatinine criteria only. For patients without chronic kidney insufficiency as reported in the medical history, we calculated a serum creatinine level using the MDRD equation as recommended by the ADQI, by solving the MDRD equation for serum creatinine assuming a glomerular filtration rate of 75 ml/minute/1.73 m^2 [24]. Baseline serum creatinine was the lowest of either creatinine at time of hospital admission or the MDRD-based estimation of baseline creatinine [23].

2.3 STATISTICAL ANALYSIS

Data are expressed as number (percentage), or median (interquartile range). Bivariate analysis was performed with the Mann-Whitney U test, Fisher exact test, and Chi2 test as appropriate. In addition, we calculated odds ratios, and sensitivity and specificity for serum urea concentration cut-offs for timing of initiation of RRT mentioned in **Table 1**. The median serum urea concentration of the whole cohort was taken as a cut-off concentration for the bivariate analysis on patients with low and high serum urea concentration. The relationship between serum urea concentration at time of initiation of RRT and in-hospital mortality was explored by construction of receiver operating characteristic curves (ROC) and calculation of the area under the ROC curve (AUC). ROC graphs are constructed by plotting sensitivity and specificity of serum urea concentration at time of initiation of RRT (as continuous variable) and serum urea cut offs that are described in literature (as categorical variables) for in-hospital mortality. An AUC of 0.5 indicates that the test has low sensitivity and specificity and performs as good as tossing a coin, and an AUC of 1 indicates an ideal test with 100% sensitivity and specificity for the outcome

variable. Multivariate logistic regression analysis was used to examine which variables were associated with mortality. Variables selected for inclusion in the regression model were these with a P value of ≤0.25 in bivariate analysis when comparing survivors and non-survivors. We analyzed for co-linearity by assessing correlation between covariates, also interaction was explored. Goodness of fit was assessed according to the method described by Hosmer and Lemeshow. Statistical significance was accepted when the P value was < 0.05. A propensity model was included in the final model. A power analysis to define sample size was performed.
A power calculation showed that 2 groups of 154 patients would be needed to give 80% power to detect a difference in mortality based on a 5% level of significance. These analyses were performed with use of the statistical software packages SPSS (SPSS for Windows, version 15.0.0), and MedCalc for Windows, version 9.6.0.0 (MedCalc Software, Mariakerke, Belgium).

The study was approved by the Ethics Committee of the Ghent University Hospital, and conducted in accordance with the declaration of Helsinki. Informed consent was waived for this study.

3. Results

3.1 BASELINE CHARACTERISTICS

From a total of 482 ICU patients who were treated with RRT, 302 patients were included in the study. A total of 180 patients who underwent RRT could not be included because of the gradual introduction of the patient database management system over the three different ICUs during the study period. Median age of the patients was 65 years (55, 73), 208 were male (68.9%). At time of ICU admission, the APACHE II score was 21 (16, 26), the SAPS II score was 45 (34, 62). One hundred twenty-nine patients (42.7%) were treated in the Surgical ICU, 100 patients (33.1%) in the Medical ICU and 73 patients (24.2%) in the Cardiac Surgery ICU. The initial mode of RRT was IHD in 162 patients (53.6%), CHD in 71 (23.5%), CVVH in 44 (14.6%), and SLEDD in 25 (8.3%). At time of initiation of RRT the SOFA score and the $SOFA_{non\text{-}renal}$ score were 10 (7, 12), and 6 (4, 8) respectively. RIFLE criteria were not met in 10 patients (3.3%), 21 patients were RIFLE-Risk (7%), 62 patients RIFLE-Injury (20.5%), and 209 patients were RIFLE -Failure (69.2%). Diuretics were administered in 135 patients (44.7%), 171 patients (56.6%) were mechanically ventilated, and 209 (69.2%) were treated with vasoactive drugs. The overall in-hospital mortality of this study cohort was 57.9 %.

3.2 COMPARISON OF SURVIVORS AND NON-SURVIVORS

Non-survivors were older (67 vs. 64 years, P= 0.016), and sicker at time of ICU admission as illustrated by the higher APACHE II and SAPS II scores **(Table 2)**. There was no difference in mortality between patients admitted to the different ICUs. Non-survivors had a different pattern of kidney failure with at time of initiation of RRT, a lower pH, serum creatinine, RIFLE class, and serum urea concentration. There was no difference in the proportion of patients with oliguria, or patients treated with diuretics. Organ dysfunction, other than that of the kidneys, was more severe in the non-survivor group. A greater proportion was treated with vasoactive drugs, platelet count was lower, and there was a trend for a greater proportion of patients treated with mechanical ventilation. Continuous RRT modalities (CHD and CVVH) that may serve as a surrogate marker for hemodynamic instability were associated with an increased in-hospital death compared to intermittent RRT modalities (IHD and SLEDD) (85/115 [73.9%] vs. 90/187 [48.1%], p<0.001).

3.3 SERUM UREA CONCENTRATION AT TIME OF INITIATION OF RRT AS A PREDICTOR FOR OUTCOME

Patients with a low serum urea concentration were more severely ill on admission. Differentiation in low versus high serum urea concentration was based on the median serum urea concentration at initiation of RRT **(Table 2)**. Patients were more acidotic, had higher serum potassium, and a lower serum creatinine. RIFLE class was lower in patients with lower serum urea concentration. A greater proportion was

Table 1.

Studies that evaluated timing of initiation of renal replacement therapy based on low or high serum urea concentration*.

* serum urea concentration has been recalculated to serum urea concentration in mg/dL. The conversion factor for serum urea (mg/dL) to Blood Urea Nitrogen (mg/dL) is multiplying by 0.446, and the conversion factor for serum urea in mmol/L to serum urea in mg/dL is to multiply by 0.167.
** Comparison to predicted mortality based on the Liaño model.
*** There was only a serum urea concentration cut-off for the high urea group. The concentrations in the table for the 2 low serum urea concentration groups are the median serum urea concentration concentrations at time of initiation of RRT. The P value was calculated on the pooled results of the 2 groups with low serum urea concentration (low volume and high volume hemofiltration) compared to the group with late initiation.

	YEAR	N	SERUM UREA CONCENTRATION (mg/dL)		28d MORTALITY (%)		*P*
			LOW	HIGH	LOW	HIGH	
RETROSPECTIVE STUDIES ON EARLY OR LATE INITIATION							
PARSONS [9]	1961	33	<336	>448	25	88	*<0.001*
FISHER [10]	1966	162	≤336	≤448	51	77	
KLEINKNECHT [11]	1970	500	<200	>350	29	39	*<0.02*
GETTINGS [12]	1999	100	<135	>135	61	80	*0.04*
BENT [13]	2001	65	≤154		40		*0.003***
LIU [14]	2006	243	≤170	>170	35	41	*0.400*
CARL [15]	2010	147	100	≥100	52	68	*<0.05*
PROSPECTIVE STUDIES ON EARLY OR LATE INITIATION							
CONGER [16]	1975	18	<157	≥224	36	80	*0.062*
GILLUM [17]	1986	34	<135	>240	59	47	*0.732*
BOUMAN [18]***	2002	106	<98 | <102	≥224	26 | 31	25	*0.680*

Table 2.

Comparison of patients with low and high serum urea concentrations at time of initiation of renal replacement therapy and survivors and non-survivors.

CSICU | Cardiac Surgery Intensive Care Unit, MICU | Medical Intensive Care Unit, SICU | Surgical Intensive Care Unit,serum urea concentration | Blood urea nitrogen, LOSICU | Length of stay in the ICU, RRT | Renal replacement therapy, $SOFA_{NON\ RENAL}$ score | SOFA score without points for kidney insufficiency, CHD | Continuous hemodialysis, CVVH | Continuous veno-venous hemofiltration, IHD | Intermittent Hemodialysis, SLEDD | Slow Extended Daily Dialysis

	SERUM UREA CONCENTRATION ≤136 mg/dL	SERUM UREA CONCENTRATION >136 mg/dL	*P*	SURVIVORS	NON-SURVIVORS	*P*
BASELINE CHARACTERISTICS						
N	152 (50,3%)	150 (49.7%)		127 (42.1%)	175 (57.9%)	
AGE (Y)	60 (54, 73)	65 (55, 73)	*0.955*	64 (52, 72)	67 (56, 74)	***0.016***
MALE GENDER	96 (63.2%)	112 (74.7%)	***0.031***	91 (71.7%)	117 (66.9%)	*0.382*
APACHE II	21 (18, 29)	21 (16, 24)	***0.015***	20 (16, 24)	22 (17, 30)	***0.001***
SAPS II	49 (38, 67)	41 (32, 56)	***0.001***	41 (33, 51)	51 (36, 69)	***<0.001***
SEPSIS	53 (34.9%)	69 (46.0%)	*0.060*	46 (36.2%)	76 (43.4%)	*0.235*
TYPE OF ICU	——	——	——	——	——	——
CSICU	41 (56.2%)	32 (43.8%)		33 (45.2%)	40 (55.8%)	
MICU	44 (44.0%)	56 (56.0%)	*0.255*	47 (47.0%)	53 (53.0%)	*0.256*
SICU	67 (51.9%)	62 (48.1%)		47 (36.4%)	82 (63.6%)	
CHARACTERISTICS AT TIME OF INITIATION OF RRT						
LOS_{ICU} TILL RRT (D)	0.9 (0.1, 1.5)	2.8 (0.4, 6.4)	***<0.001***	1.5 (0.1, 3.2)	1.3 (0.3, 3.5)	*0.575*
MODALITY OF RRT	——	——		——	——	——
CHD	57 (37.5%)	14 (9.3%)		17 (13.4%)	54 (30.9%)	
CVVH	25 (16.4%)	19 (12.7%)	***<0.001***	13 (10.2%)	31 (17.7%)	***<0.001***
IHD	58 (38.2%)	104 (69.2%)		85 (66.9%)	77 (44.0%)	
SLEDD	12 (7.9%)	13 (8.7%)		12 (9.4%)	13 (7.4%)	
RIFLE CLASS	——	——	——	——	——	——
No RIFLE class	9 (5.1%)	1 (0.7%)		6 (4.7%)	4 (2.3%)	
Risk	18 (11.8%)	3 (2.0%)	***<0.001***	3 (2.4%)	18 (10.3%)	***<0.001***
Injury	50 (32.9%)	12 (8.0%)		11 (8.7%)	51 (29.1%)	
Failure	75 (49.3%)	134 (89.3%)		107 (84.3%)	102 (58.3%)	
$Creatinine_{MAX}$ (mg/dL)	2.92 (2.03, 4.29)	4.51 (3.55, 5.95)	***<0.001***	4.77 (3.71, 6.27)	3.18 (2.26, 4.10)	***<0.001***
$Urea_{MAX}$ (mg/dL)	90 (70, 114)	195 (156, 262)	***<0.001***	141 (101, 206)	130 (83, 184)	*0.038*
Oliguria	74 (48.7%)	60 (40.0%)	*0.129*	57 (44.9%)	77 (44.0%)	*0.879*
Diuretic therapy	61 (40.1%)	74 (49.3%)	*0.108*	57 (44.9%)	78 (44.6%)	*0.957*
pH_{MIN}	7.22 (7.13, 7.29)	7.26 (7.19, 7.33)	***0.001***	7.27 (7.21, 7.33)	7.22 (7.13, 7.29)	***<0.001***
$Potassium_{MAX}$ (mmol/L)	5.1 (4.6, 5.8)	4.9 (4.3, 5.4)	***0.030***	5.0 (4.3, 5.4)	5.0 (4.5, 6.0)	***0.040***
$Phosphorus_{MAX}$ (mg/dL)	6.2 (4.7, 7.8)	6.3 (4.8, 7.8)	*0.948*	6.1 (4.7, 7.6)	6.4 (4.8, 7.9)	*0.220*
Mechanical ventilation	83 (54.6%)	88 (58.7%)	*0.476*	65 (51.2%)	106 (60.6%)	*0.104*
PaO_2/FiO_2	101 (126.0)	133 (100.1)	*0.198*	104 (66, 156)	124 (79, 190)	*0.111*
Vaso-active drugs	113 (74.3%)	96 (64.0%)	*0.052*	70 (55.1%)	139 (79.4%)	***<0.001***
Platelets ($x10^3/\mu L$)	120 (79, 178)	131 (74, 210)	*0.375*	138 (93, 211)	118 (65, 181)	***0.015***
Bilirubin (mg/dL)	1.3 (0.6, 2.6)	1.3 (0.5, 4.3)	*0.827*	1.4 (0.5, 2.7)	1.3 (0.6, 3.2)	*0.248*
SOFA score	9 (6, 13)	10 (6,13)	*0.476*	9 (5,12)	10 (7,13)	***0.012***
$SOFA_{NON\ RENAL}$ score	6 (4, 8)	6 (4, 9)	*0.902*	5 (3,7)	7 (4, 9)	***<0.001***
OUTCOME						
MORTALITY	95 (62.5%)	80 (53.3%)	*0.107*			

hemodynamically unstable, as illustrated by the greater proportion of treatments with a continuous RRT modality and the clear trend for more patients on vasoactive drugs. There was a trend for worse outcome in patients with low serum urea concentration.

3.3.1. Bivariate analysis We explored the different serum urea cut-offs as reported in literature **(Table 1)** in our cohort. In present time, there is a trend to initiate RRT earlier in the course of AKI. Therefore, we also analysed two other serum urea concentration cut-offs (serum urea concentration 70 mg/dL and 100 mg/dL). None of the serum urea concentration cut-offs, except serum urea > 100 **[15]** and >170 mg/dL **[14]** and were associated with mortality in bivariate analysis **(Table 3)**. However, in our study cohort, patients with higher serum urea had lower instead of higher, in-hospital mortality. Serum urea concentration at time of initiation of RRT, measured as a continuous variable, as well as the different serum urea concentration cut-offs that are mentioned in literature **(Table 1)** had poor sensitivity and specificity, and therefore low AUC for the ROC curves for prediction of in-hospital mortality **(Fig. 1 and 2)**.

3.3.2. Multivariate analyses We evaluated if serum urea concentration at time of initiation of RRT was associated with in-hospital mortality. We analyzed different multivariate logistic regression models **(Table 4)**. In model 1 covariates used for adjustment were age, APACHE II score and type of ICU (medical ICU, surgical ICU, and cardiac surgery ICU). Covariates used for adjustment in model 2 were variables in model 1, and variables at time of initiation of RRT: modality of RRT, $SOFA_{non\text{-}renal}$, RIFLE class, lowest pH, maximum potassium and phosphorus. Finally, we included a propensity score in the multivariate model to correct for possible bias leading to some patients put earlier in RRT. In our propensity model we included following data: sex, APACHE II, RIFLE, ICU type, urine output (24hours) and creatinine on admission. Including this propensity score in our model we still found no association between serum urea and in-hospital mortality **(Table 5, and Fig. 3)**. We performed a sensitivity analysis, and analysed the same model in subgroups of patients with low and high serum urea concentration. This demonstrated in the two subgroups that serum urea concentration and mortality were not associated (data not shown).

4. Discussion

Timing of initiation of RRT for AKI and outcome have been traditionally linked to serum urea concentration cut-offs. This could not be confirmed in our dataset of ICU patients with AKI who were treated with RRT. Serum urea concentration at time of initiation of RRT as a continuous variable was also not associated with in-hospital mortality.

Despite the limitations of serum urea concentration as a marker for kidney function **[25]**, it is traditionally used as a surrogate marker for severity and duration of the AKI episode. Several studies dating back from the 1960s until 2001 suggested that certain serum urea concentration cut-offs were predictive for in-hospital mortality. In the 1960's, Teschan et al. introduced the concept of prophylactic dialysis based on serum urea concentration, i.e. initiation of RRT before occurrence of uremic symptoms **[26]**. Several retrospective studies published from then on, suggested that initiation of RRT at lower serum urea concentrations or more early in the course of

Fig. 1.

Receiver Operating Characteristic curve for serum urea concentration at time of initiation of RRT and in-hospital mortality.

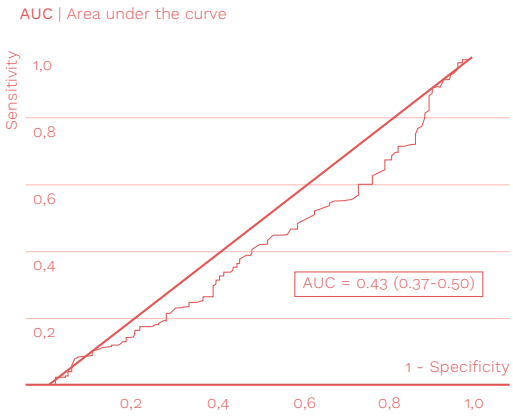


Table 3.

Risk for hospital mortality and predictive value in our study cohort when traditionally used blood urea nitrogen cut-off levels (indicated by the first author) are applied.

SERUM UREA CONCENT. CUT-OFF (MG/DL)	SOURCE AUTHOR	≤ CUT-OFF		≤ CUT-OFF		*P*	SENSI-TIVITY	SPECI-FICITY
		MORTALITY N (%)	MEDIAN SERUM UREA CONCENT. (MG/DL)	MORTALITY N (%)	MEDIAN SERUM UREA CONCENT. (MG/DL)			
75	STUDY COHORT	31 (68,9)	59,0	144 (56,2)	145,5	*0,113*	82,3%	11,1%
100	CARL [15]	67 (69,1)	78,0	108 (52,9)	164,5	*0,008*	61,7%	23,8%
135	GETTINGS [12]	94 (63.1)	89,0	81 (53.3)	193,5	*0.085*	46.3%	43.7%
157	CONGER [16]	117 (61.3)	99,0	58 (52.7)	216,5	*0.149*	33.1%	58.7%
170	LIU [14]	126 (62.1)	103,0	49 (50.0)	228,5	*0.047*	28.0%	61.1%
200	KLEINKNECHT [11]	141 (60.8)	116,0	34 (49.3)	266,0	*0.089*	19.4%	72.2%
224	GILLUM [17]	149 (59.4)	123,0	26 (52.0)	299,0	*0.335*	14.9%	81.0%
240	BOUMAN [18]	152 (59.4)	125,0	23 (51.1)	301,0	*0.300*	13.1%	82.5%
336	PARSONS / FISCHER [9,10]	170 (58.6)	133,0	5 (45.5)	424,0	*0.385*	2.9%	95.2%

Table 4.

Association of serum urea at time of initiation of renal replacement therapy. Comparison of univariate analysis and different multivariate logistic regression models.

Covariates used for adjustment in Model 1
age, APACHE II score, type of ICU (medical ICU, surgical ICU, and cardiac surgery ICU).
Covariates used for adjustment in Model 2
Variables in Model 1, and variables at time of initiation of RRT: modality of RRT, SOFA non-renal, RIFLE class, lowest pH, maximum potassium and phosphorus.
Covariates used for adjustment in Model 3
Variables in Model 2, and a propensity score.

	OR	95% CI	*P*
UNIVARIATE ANALYSIS	0.800	0.614, 1.042	*0.970*
MULTIVARIABLE ANALYSIS			
Model 1	0.793	0.598, 1.053	*0.109*
Model 2	1.202	0.841, 1.716	*0.313*
Model 3	1.206	0.838, 1.733	*0.313*

Model 1 Goodness of fit (Hosmer and Lemeshow) Chi2 = 7.079, df = 8, P = 0.528.
Overall percentage correct predicted = 62.5%
Model 2 Goodness of fit (Hosmer and Lemeshow) Chi2 = 4.579, df = 8, P = 0.801.
Overall percentage correct predicted = 75.3%
Model 3 Goodness of fit (Hosmer and Lemeshow) Chi2 = 9.388, df = 8, P = 0.311.
Overall percentage correct predicted = 73.7 %

AKI indeed were associated with improved outcome (Table 1) [9-14]. Although the first prospective randomized study on this topic did not reach statistical significance, a clear trend supported this concept [16]. Two other prospective studies could not demonstrate that early initiation of RRT at lower serum urea concentrations was associated with better outcomes [17,18].

Despite this, the current paradigm is that timing of initiation of RRT for AKI may be based on a series of clinical and biochemical variables, including certain serum urea concentrations. Also, a recent meta-analysis concluded that early initiation of RRT may be associated with improved survival. Thirteen of the 23 included studies used serum urea as a criterion for initiation of RRT [27]. In 2008 the AKIN consensus group proposed, based on the existing literature, serum urea > 224 mg/dL as an absolute and serum urea > 170 mg/dL as a relative indication for initiation of RRT [8].

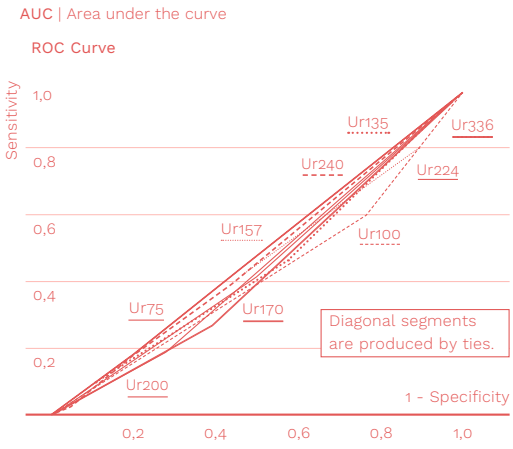
Our findings shed new light on this discussion. Serum urea was not a good predictor for worse outcome in ICU patients with AKI. Several elements may be involved in these findings.

First, the serum urea concentration paradigm for timing of initiation of RRT is based on limited evidence and mostly old studies. The patient cohorts described in these hallmark studies are not comparable to the AKI patients we are nowadays treating. The prospective studies on this topic have been performed 10 - 38 years ago, are underpowered, and include very specific cohorts of patients that do not have necessarily external validity. Second, serum urea concentration is determined by numerous other variables that have no relation to kidney function, such as catabolism, administration of corticosteroids, gastrointestinal bleeds, etc. Also, increased serum urea concentrations very likely have limited biological effects as observed in current clinical conditions [28,29]. Third, patients with higher serum urea concentration at time of initiation of RRT in our cohort were less severely ill compared to the low serum urea concentration cohort.

In most patients RRT will be initiated immediately and early in the course of AKI for indications such as severe acid-base disturbances, severe hyperkalaemia or fluid overload. In this setting, serum urea concentration at time of initiation of RRT is relatively low, although this group of patients is severely ill and has worse prognosis. The most plausible explanation for the absence of a relation between serum urea concentration and outcome is the fact that RRT is initiated early in the group of more severely ill patients, i.e. before serum urea concentration has had the time to rise. In contrast to our findings concerning the impact of serum urea concentrations on outcome, multivariate analysis

Fig. 2.

Receiver Operating Characteristic curves for different *historical* serum urea concentration cut-offs at time of initiation of RRT and in-hospital mortality applied to our study cohort.



SOURCE /AUTHOR	SERUM UREA CONCENTRATION CUT-OFF (mg/dL)	AUC	95% CI
STUDY COHORT	75	0.47	0.40, 0.53
CARL [15]	100	0.43	0.36, 0.49
GETTINGS [12]	135	0.45	0.38, 0.52
CONGER [16]	157	0.46	0.39, 0.53
LIU [14]	170	0.45	0.38, 0.51
KLEINKNECHT [11]	200	0.46	0.39, 0.53
GILLUM [17]	224	0.48	0.41, 0.55
BOUMAN [18]	240	0.48	0.41, 0.55
PARSONS /FISCHER [9,10]	336	0.49	0.42, 0.56

demonstrated that factors as age and severity of non-renal illness did have an important impact on mortality.

Finally, our data revealed an inverse association between increasing RIFLE class and outcome.This may seem against intuition, but is in line with current literature. Increasing severity of maximum RIFLE class has been shown repeatedly to be associated with a stepwise increase in mortality and length of ICU stay [23,30-32]. However, RIFLE class determined at time of RRT initiation was never associated with outcome [33,34]. Serum creatinine at time of initiation of RRT has an inverse relationship with outcome, possibly explained by the fact that serum creatinine also serves as a surrogate marker for other comorbid disease that may impact outcome. For instance, older patients with chronic disease or patients who were already hospitalized for longer time, have less muscle mass, leading to lower creatinine concentration for a given glomerular filtration rate [25,35].

This is to the best of our knowledge the only study that exclusively focuses on the prognostic value of serum urea concentration for timing of initiating of RRT in general ICU patients, as recently recommended by AKIN. Subsequently, this study meticulously evaluates the numerous and widespread used serum urea concentration cut-offs recommended in literature. The strengths of this study include the high quality of the electronically collected data, the fact that recent data were collected on a relative large and well-powered study population that was representative for a tertiary ICU in a developed country, and that in-hospital mortality (and not ICU mortality) was assessed as outcome.

The study also includes several limitations. First, its retrospective design can only be hypothesis generating on the topic of timing of initiation of RRT. Multivariate analysis is a tool that may correct for the observational design of the study. But such an analysis is only as good as the type and quality of the covariates that are entered into the model. Therefore we analysed different multivariate logistic regression models. We also included a propensity score to correct for bias. Our database consisted of data on baseline characteristics of the patients, and data recorded at time of initiation of RRT. However, covariates that were not available such as volume balance, may also have had an important impact on outcome [36].

Fig. 3.

Adjusted risk for in-hospital death for the different serum urea concentration cut offs as mentioned in literature (indicated by the first author), applied to our study cohort. A multivariate logistic regression analysis with adjustment for the same covariates as in table 5.

* relative indication AKIN
** absolute indication AKIN

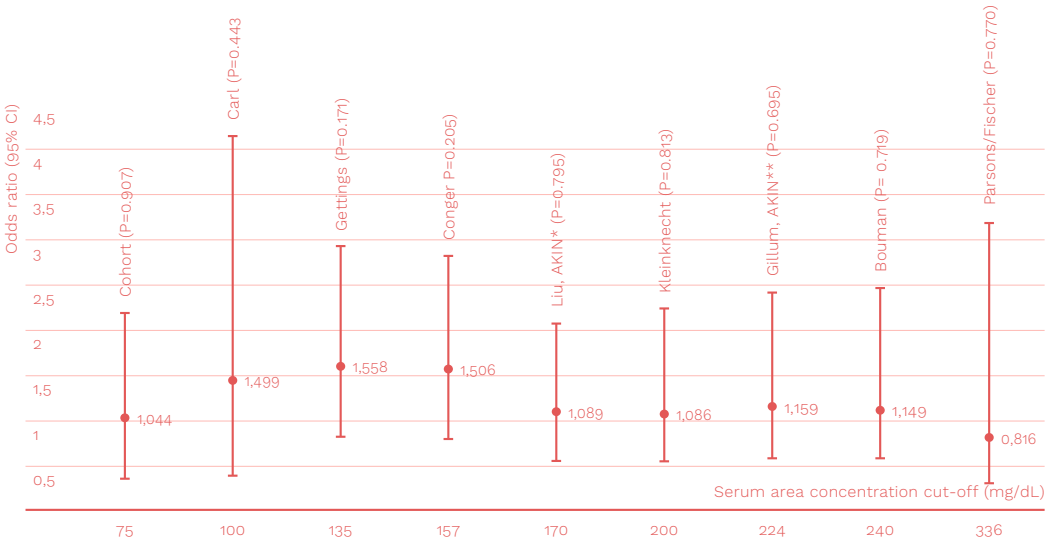


Table 5.

Covariate adjusted association of serum urea concentration with in-hospital death. A multivariate logistic regression model with inclusion of a propensity score.

	OR	95% CI	P
DEMOGRAPHIC DATA	——	——	——
Age (per year)	1.049	1.025, 1.073	***<0.001***
APACHE II (per point)	1.028	0.961, 1.099	*0.424*
TYPE OF ICU (ref. cardiac surgery ICU)	——	——	*0.352*
Medical ICU	1.116	0.397, 3.138	*0.835*
Surgical ICU	1.662	0.756, 3.652	*0.206*
urea (per g/dL)	1.206	0.838, 1.733	*0.313*
RIFLE CLASS (ref. not fulfilling RIFLE classification criteria)	——	——	***<0.001***
Risk	7.976	1.059, 60.069	***0.044***
Injury	5.146	0.916, 28.912	*0.063*
Failure	0.770	0.153, 4.017	0.770
RRT MODALITY (ref. CHD)	——	——	0.091
CVVH	1.047	0.341, 3.215	*0.936*
IRRT	0.425	0.168, 1.078	*0.072*
SLEDD	0.387	0.110, 1.359	*0.139*
SOFA NON- RENAL (per point)	1.162	1.053, 1.282	***0.003***
SEPSIS	1.220	0.527, 2.825	*0.642*
POTASSIUM (per mmol/L)	1.383	1.005, 1.902	***0.047***
pH	2.114	0.133, 33.697	*0.596*
PHOSPHORUS (per mg/dL)	1.076	0.946, 1.225	*0.265*

Goodness of fit (Hosmer and Lemeshow) Chi2 = 9.388, df = 8, P = 0.311.
Overall percentage correct predicted = 73.7%

Also, RIFLE class was assessed on creatinine criteria only as we did not have detailed urine output data necessary for classifying. The results on RIFLE could be different when urine output was used as a criterium. However, this limitation is present in the majority of studies on the epidemiology of AKI [31,37]. Second, similar to the majority of the studies on this topic, all patients in our study received RRT. Including AKI patients without RTT could have led to different conclusions. For instance, patients with low severity of AKI, low serum urea, and without severe multiple organ dysfunction syndrome may have recovered AKI without RRT. Also, AKI patients with high serum urea levels may have died without RRT. In addition, initiation of RRT was in part based on serum urea concentrations as we follow consensus recommendations. However, the sensitivity analysis in the low and high serum urea concentration group could not demonstrate a difference in outcomes, suggesting that this bias was only limited. Further, the broad range of serum urea concentrations, with a median concentration of 136 mg/dL permits to evaluate all urea cut-offs mentioned in literature. Third, because our patients database management system was introduced gradually over the 3 different ICUs during the study period, we couldn't study all patients who underwent RRT. However, as we could not demonstrate a difference in outcome or serum urea concentration between the different ICUs, it is unlikely that this has influenced the results profoundly. Finally, the data reflect the practice from a single centre, and may therefore not be applicable to other settings where other practice protocols for treatment of ICU patients with AKI are used.

Our findings highlight the need for a well-set-up prospective randomized trial on the timing of initiation of RRT. The design of such a trial needs careful consideration. We propose that patients in such a study are stratified according to severity of illness, with different criteria for initiation of RRT in the different strata. Given the arguments discussed above, we do not feel that serum urea concentration should still be a criterion in this study. RIFLE or AKI criteria have been proposed as alternatives [8], and are probably more accurate in differentiating early and less severe from progressed and more severe AKI.

In conclusion, this study suggests that serum urea concentration cut-offs at time of initiation of RRT, as they have been used from the early days of acute RRT, and as they are actually recommended, have no predictive value for in-hospital mortality in severely ill ICU patients with AKI.

ACKNOWLEDGEMENTS

E.A.J.H. is a Senior Clinical Investigator of the Research Foundation, Flanders (Belgium) (Fonds Wetenschappelijk Onderzoek). This study was conducted without financial support.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

[1] Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294:813-8.

[2] Hoste EA, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? Crit Care Med 2008; 36:S146-51.

[3] Hoste EA, De Corte W. Epidemiology of AKI in the ICU. Acta Clin Belg Suppl 2007:314-7.

[4] Metnitz PG, Krenn CG, Steltzer H, et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 2002; 30:2051-8.

[5] Metcalfe W, Simpson M, Khan IH, et al. Acute renal failure requiring renal replacement therapy: incidence and outcome. QJM 2002; 95:579-83.

[6] Waikar SS, Curhan GC, Wald R, et al. Declining mortality in patients with acute renal failure, 1988 to 2002. Journal of the American Society of Nephrology 2006; 17:1143-50.

[7] Goss CH, Brower RG, Hudson LD, et al. Incidence of acute lung injury in the United States. Crit Care Med 2003; 31:1607-11.

[8] Gibney N, Hoste E, Burdmann EA, et al. Timing of initiation and discontinuation of renal replacement therapy in AKI: unanswered key questions. Clin J Am Soc Nephrol 2008; 3:876-80.

[9] Parsons FM, Hobson SM, Blagg CR, et al. Optimum time for dialysis in acute reversible renal failure. Description and value of an improved dialyser with large surface area. Lancet 1961; 1:129-34.

[10] Fischer RP, Griffen WO, Jr., Reiser M, et al. Early dialysis in the treatment of acute renal failure. Surg Gynecol Obstet 1966; 123:1019-23.

[11] Kleinknecht D, Jungers P, Chanard J, et al. Uremic and non-uremic complications in acute renal failure: Evaluation of early and frequent dialysis on prognosis. Kidney Int 1972; 1:190-6.

[12] Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. Intensive Care Med 1999; 25:805-13.

[13] Bent P, Tan HK, Bellomo R, et al. Early and intensive continuous hemofiltration for severe renal failure after cardiac surgery. Ann Thorac Surg 2001; 71:832-7.

[14] Liu KD, Himmelfarb J, Paganini E, et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol 2006; 1:915-9.

[15] Carl DE, Grossman C, Behnke M, et al. Effect of timing of dialysis on mortality in critically ill, septic patients with acute renal failure. Hemodialysis international. International Symposium on Home Hemodialysis 2010; 14:11-7.

[16] Conger JD. A controlled evaluation of prophylactic dialysis in post-traumatic acute renal failure. J Trauma 1975; 15:1056-63.

[17] Gillum DM, Dixon BS, Yanover MJ, et al. The role of intensive dialysis in acute renal failure. Clin Nephrol 1986; 25:249-55.

[18] Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, et al. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med 2002; 30:2205-11.

[19] Reynvoet E, Vandijck DM, Blot SI, et al. Epidemiology of infection in critically ill patients with acute renal failure. Crit Care Med 2009; 37:2203-9.

[20] Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/ North American multicenter study. JAMA 1993; 270:2957-63.

[21] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818-29.

[22] Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707-10.

[23] Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10:R73.

[24] Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care 2004; 8:R204-R12.

[25] Lameire N, Hoste E. Reflections on the definition, classification, and diagnostic evaluation of acute renal failure. Curr Opin Crit Care 2004; 10:468-75.

[26] Teschan PE, Baxter CR, O'Brien TF, et al. Prophylactic hemodialysis in the treatment of acute renal failure. Ann Intern Med 1960; 53:992-1016.

[27] Seabra VF, Balk EM, Liangos O, et al. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. Am J Kidney Dis 2008; 52:272-84.

[28] Johnson WJ, Hagge WW, Wagoner RD, et al. Effects of urea loading in patients with far-advanced renal failure. Mayo Clin Proc 1972; 47:21-9.

[29] Vanholder R, De Smet R, Glorieux G, et al. Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int 2003; 63:1934-43.

[30] Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Critical Care Medicine 2006; 34:1913-7.

[31] Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. Kidney International 2008; 73:538-46.

32. Ostermann M, Chang RW. Acute renal failure in ICU - Evaluation of the RIFLE classification. Critical Care Medicine 2005; 33:A73-A.

[33] Maccariello E, Soares M, Valente C, et al. RIFLE classification in patients with acute kidney injury in need of renal replacement therapy. Intensive Care Medicine 2007; 33:597-605.

[34] Bell M, Liljestam E, Granath F, et al. Optimal follow-up time after continuous renal replacement therapy in actual renal failure patients stratified with the RIFLE criteria. Nephrology Dialysis Transplantation 2005; 20:354-60.

[35] Hoste EA, Damen J, Vanholder RC, et al. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. Nephrol Dial Transplant 2005; 20:747-53.

[36] Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008; 12:R74.

[37] Bellomo R, Kellum JA, Ronco C. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. Intensive Care Medicine 2007; 33:409-13.

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Severe lactic acidosis in critically ill patients with acute kidney injury treated with renal replacement therapy.

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PUBLISHED IN
J Crit Care. 2014 Aug;29(4):650-5.

PURPOSE

SLA is frequent in ICU patients with AKI treated with RRT. The aim of the study is to describe the epidemiology of SLA in this setting.

MATERIALS AND METHODS

An observational single center cohort analysis was performed on AKI patients treated with RRT. At initiation of RRT, SLA patients (serum lactate concentration >5 mmol/l and pH<7.35) were compared with non-SLA patients.

RESULTS

Of the 454 patients dialyzed during the study period, 342 patients matched inclusion criteria (116 with and 226 patients without SLA). In SLA patients, lactate stabilized/decreased in 69.7% at 4 hours ($p=0.001$) and in 81.8% during the period of 4 to 24 hours ($p<0.001$) after initiation of RRT. Mortality during this 24-hours period was 31.0%. ICU mortality was 83.6% compared to 47.3% in non-SLA patients. Initial lactate concentration was not related to ICU mortality in SLA patients.

CONCLUSIONS

SLA was frequent in AKI patients treated with RRT. SLA patients were more severely ill and had higher mortality compared with patients without. During the first 24 hours of RRT, a correction of lactate concentration and acidosis was observed. In SLA patients lactate concentration at initiation of RRT was not able to discriminate between survivors and nonsurvivors.

1. Introduction

Serum lactate has been widely considered an important biomarker for evaluation of hemodynamic status in critically ill patients. It is the reflection of the balance between lactate production and clearance. In basal metabolic conditions lactate levels vary between 0.5 and 1 mmol/L. Historically, hyperlactatemia refers to serum lactate concentration above 2 mmol/L but lower than 5 mmol/L. As a different clinical entity lactic acidosis is defined as a blood lactate level higher than 5 mmol/l and pH less than 7.35. Cohen further classified lactic acidosis based on the presence (type A) or absence (type B) of tissue hypoxia [1, 2]. The relationship between tissue hypoxia and formation of lactic acid was already demonstrated in the late 1800's by Araki and Zillessen [3]. Apart from the underlying cause of lactic acidosis, this may in part be explained by the deleterious direct effects of acidosis such as decreased myocardial contraction by Na+/H+ exchange activation, decreased response to vasopressors due to a down regulation of beta receptors and impaired intracellular calcium signalling, effects on endothelial function and effects on the inflammatory response [4-10]. Although lactate is a non-toxic molecule, the increase in concentration indicates important alterations in homeostasis and is, therefore, associated with increased mortality [11, 12]. Often, lactic acidosis is associated with AKI and since the early 1960's, RRT has been used for correction of acid-base homeostasis as an adjunct to the treatment of the underlying cause [13]. Where hemodynamic instability is observed, continuous RRTs are effective at correcting the observed acidosis [14, 15]. This is reflected in reviews [16, 17] and the recent consensus guidelines by the AKIN and the (KDIGO group, which considers life-threatening metabolic acidosis a possible indication for RRT [18, 19].

⟶ KEY MESSAGE

SLA is common in AKI-RRT patients but lactate concentration at initiation of RRT is not able to discriminate between survivors and non-survivors.

Lactate has a molecular weight of 90 Da, similar to urea (60 Da), and, as such, is easily removed by RRT. The relatively low molecular weight makes diffusion based therapies particularly attractive, whereas it can be expected also to remove other anions associated with lactate acidosis including isocitrate, α-ketoglutarate and malate [20].

In the presence of SLA, many clinicians hesitate to initiate RRT based on the hypothesis that short-term benefit cannot be achieved and that the administration of RRT exposes patients to the harm of RRT, and administration of bicarbonate by dialysis may even worsen clinical state. Indeed, despite over 50 years of experience with the use of RRT in AKI patients with SLA, data on this topic are scarce. The most recent study was published over 15 years ago, where Hilton et al [21] found that patients with SLA and AKI supported with bicarbonate buffered hemofiltration had a mortality of 71.5%. Therefore, the aim of this study is to describe the current epidemiology of SLA in a cohort of critically ill patients with AKI treated with RRT. In addition, we evaluate factors that may influence outcome in patients with SLA.

2. Materials and Methods

We performed an observational single centre cohort analysis over a three-year period (August 2004 – July 2007) on intensive care unit (ICU) patients who had AKI treated with RRT. In this cohort we compared patients with SLA at time of initiation of RRT (pH < 7.35 or treatment with $NaHCO_3$ to correct acidosis, and a serum lactate concentration ≥ 5 mmol/L) to patients without SLA (serum lactate concentration ≤ 5 mmol/L). The adult ICU of the Ghent University Hospital comprises a 22 bed surgical ICU, a 14 bed medical ICU, a 6 bed burn ICU and an 8 bed cardiac surgery ICU. These ICUs function independently with their own policy concerning indications for RRT and modalities used, depending on the attending intensivists and nephrologists. We included all ICU patients, age 15 year and older who had AKI treated with RRT. During the study period, the electronic PDMS was gradually introduced. Only patients who were registered in the PDMS were included in the study. Patients who had SLA on the day of initiation of RRT but had a decrease in serum lactate at time of initiation of RRT were excluded. Treatment episodes with peritoneal dialysis, a modality seldom used in our ICUs in selected patients with cirrhosis or decompensated heart failure, were also excluded. Indications for RRT, as well as the modality chosen were determined in consensus between the attending intensivists and nephrologists [22] (treatment modalities used are presented in **Supplemental Table E1**). In subanalysis, we compared patients with SLA to ICU patients without lactic acidosis who were initiated on RRT for AKI. Also, we compared patients who were treated with diffusive IHD, SLEDD, CVVHD versus convective CVVH RRT modalities and patients who underwent continuous (CVVH, CVVHD) versus intermittent (IHD, SLEDD) RRT.

2.1 DATA COLLECTION

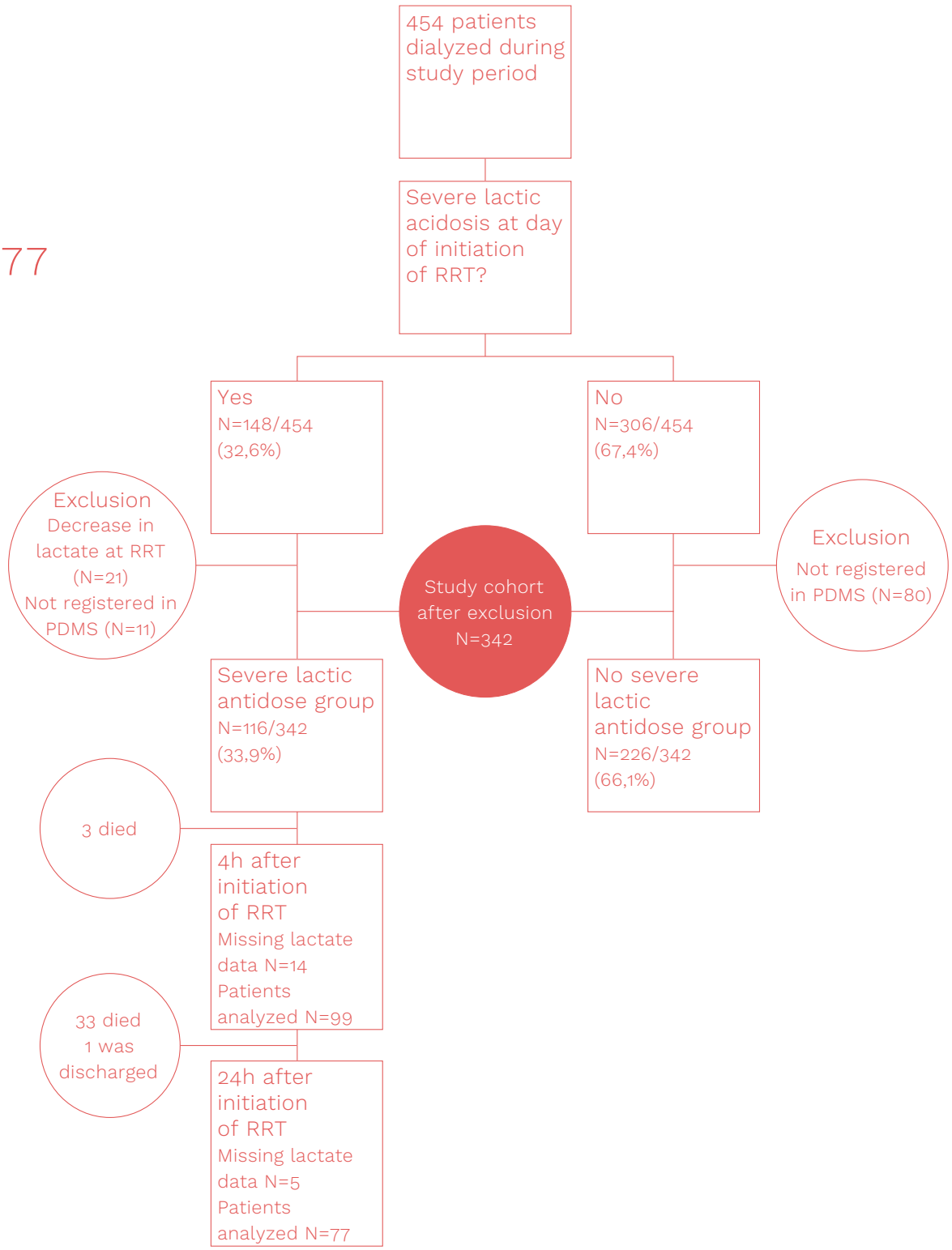
Demographic data were retrieved from the electronic hospital database and the paper medical files, laboratory data from the laboratory database and patient data from the electronic ICU PDMS or paper medical file. Data on comorbidity and diagnostic categories were retrieved from the electronic hospital administration International Classification of Diseases, Ninth Revision, coding system. Severity of illness was assessed at time of ICU admission by the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score (based on data recorded during the first 24 hours of ICU admission) [23].

At time of initiation of RRT, severity of illness was assessed by parameters of organ dysfunction. Serum concentrations of lactate and bicarbonate, pH, blood pressure and the use of vasoactive medication were retrieved at time of initiation of RRT and 4 and 24 hours after initiation of RRT. Serum concentrations of creatinine, urea, bilirubin and thrombocytes were recorded at initiation of RRT and 24 hours later.

Fig. 1.

Patient flow chart.

PDMS | Patient Data Management System



2.2 STATISTICAL ANALYSIS

Data are expressed as number (percentage), or median (interquartile range). Bivariate analysis was performed with the Mann-Whitney U test for continuous variables and the Fisher exact test or Chi2 test for categorical variables as appropriate. Multivariate logistic regression analysis was used to examine the association of SLA and modality of RRT with mortality. Variables selected for inclusion in the regression model were these with P ≤ .25 in bivariate analysis when comparing survivors and non-survivors. We analyzed for co-linearity by assessing correlation between covariates; also, interaction was explored. Goodness of fit was assessed according to the method described by Hosmer and Lemeshow. In addition, we evaluated sensitivity and specificity for the model by the area under the curve of a receiver operating characteristic curve. Statistical significance was accepted when the P value was less than .05 (double sided). In order to explore the impact of patients with missing lactate concentration at time points 4 hours and 24 hours after initiation of RRT, a sensitivity analysis was performed in which we compared baseline characteristics and outcomes with those of patients with complete data. These analyses were performed with use of the statistical software packages SPSS (SPSS for Windows, version 19.0.0).

The study was approved by the Ethics Committee of the Ghent University Hospital RRT (Ghent University Ethical Committee, study B67020072642, date: 4/10/2007) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived for this study.

3. Results

During the 3-year study period, 454 patients with AKI were treated with RRT. On the day of initiation of RRT 148 patients (32.6%) were diagnosed with SLA. Thirty-two of these patients did not meet inclusion criteria (11 patients were not registered in PDMS because of its gradual introduction, 21 patients showed a decrease of serum lactate on time of initiation of RRT). We registered 306 patients without SLA on the day of initiation of RRT. After exclusions, the study cohort comprised 342 patients: 116 patients (33.9%) with SLA and 226 patients (66.1%) without SLA **(Fig. 1)**.

The baseline characteristics of the study cohort are described in **Table 1**. Median age was 65 years, and 67.5 % were male. Severity of illness as illustrated by the APACHE II score at time of ICU admission was high (median 21; IQR 16-27). The majority of patients were admitted to a surgical or cardiac surgery ICU. Patients with SLA were more severely ill compared to patients without as illustrated by the higher APACHE II score at time of ICU admission, and at time of initiation of RRT, they had serum higher bilirubin, lower platelet count, more frequent use of continuous RRT and higher need for mechanical ventilation and vasoactive therapy. Only 24.6% of patients with SLA had sepsis as admission diagnosis reported in the hospital administration system **(Table 1)** On the other hand, at time of initiation of RRT, as much as 82.8% were on mechanical ventilation, and 85.3% were on vasopressor therapy. Also, platelet count of patients with SLA was decreased to a median of 77.5 x 10E9/L. This may indicate that the actual proportion of patients who had severe sepsis/septic shock at time of initiation of RRT actually was higher.

3.1 OUTCOMES

Patients with SLA had a shorter length of ICU and hospital stay but a higher crude ICU and hospital mortality (83.6% vs. 47.3%, p<0.001 and 83.6% vs. 47.8%, p<0.001 respectively) **(Table 1)**. In the SLA cohort, 3 patients (2.6%) died within 4 hours and 33 patients (28.4%) died within the period between 4 to 24 hours after initiation of RRT **(Fig. 1)**. In a multivariate logistic regression model, we found that, after adjustment for confounders SLA was associated with increased hospital mortality (odds ratio 3.42 (95% confidence interval 1.41 – 8.31; P =0.007)) (detailed analysis shown in **Supplemental Table E2**).

A detailed comparison between ICU survivors and nonsurvivors among the lactic acidosis group is presented in **Table 2**. Nonsurvivors were older, had higher serum

urea and serum creatinine at time of initiation of RRT. Other baseline characteristics were similar between groups.

3.1.1. Evolution of serum lactate concentration, pH and bicarbonate during the 24 h study period Serum lactate concentration showed a significant decrease at 4 and 24 hours after initiation of RRT ($P < .001$, **Fig. 2**). Bicarbonate concentration and pH significantly increased at 4 and 24 hours (all $P < 0.001$, **Fig. 2**, bicarbonate not shown). We found that 69.7% of patients had a decrease or stabilisation of serum lactate concentration after 4 hours of RRT **(Supplemental Table E3)**. These individuals were older, less acidotic, and a lower proportion was mechanically ventilated compared to patients whose lactate increased over this period. After 24 hours of RRT, serum lactate had decreased in 81.8% of patients. Baseline characteristics and outcomes were similar between patients with an increase or a decrease/ stabilization of serum lactate over the 24-hour study period. Importantly, serum lactate concentration at time of initiation of RRT was not different between patients who had a decline or an increase of lactate during the 4- and 24-hour study period.

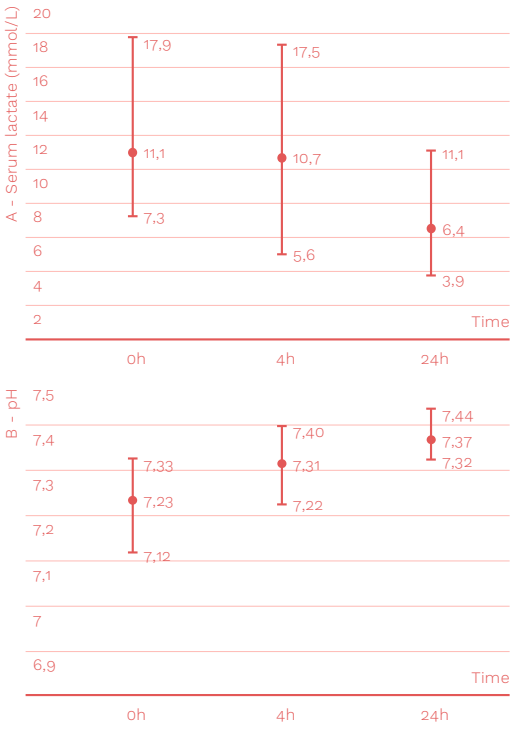
3.1.2. Convective versus diffusive RRT, and continuous versus intermittent RRT modalities Compared with convection, diffusive therapy was used in 75.0% of patients. Patients treated with diffusive RRT were more frequently admitted to the surgical and medical ICU and had lower serum creatinine and bicarbonate. Patients who underwent intermittent RRT (23.3%) had a lower serum lactate and a higher pH and higher bilirubin compared to patients who were treated with continuous RRT (**Supplemental Table E4**).

There were no differences in the evolution of serum lactate concentration during the 24-hour study period comparing patients treated with diffusive and convective modality or continuous vs intermittent modalities (data not shown). In addition, outcomes were comparable in these two subgroup analyses **(Supplemental Table E4)**. Furthermore, after correction for age, gender, APACHE II, pH, urea and serum creatinine, continuous RRT (compared with Intermittent RRT) and diffusive RRT (compared with convective RRT) were not associated with hospital mortality (**Supplemental Table E5**).

3.1.3. Sensitivity analysis Not all patients who were alive had serum lactate concentration measured at 4 and 24 hours after initiation of RRT. To explore if this introduced a bias that could impact on this analysis, we compared patients with complete and incomplete datasets as an additional sensitivity analysis. Here, we found no differences in baseline characteristics and outcome between patients who had lactate concentration recorded 4 hours, respectively 24 hours after initiation of RRT (n = 99 resp. n = 77) and those who had not (n = 14 respectively n = 5).

Fig. 2.

Evolution of serum lactate concentration and pH over time in 24-hour survivors and nonsurvivors. A, Evolution of serum lactate concentration over time. B, Evolution of pH over time. Data are expressed as median and interquartile range.



4. Discussion

In this cohort of critically ill patients with AKI treated with RRT, one-third had SLA at time of initiation of RRT. Compared with patients without SLA, these patients had higher ICU mortality and were more severely ill. Multivariate regression analysis confirmed the well-known association between SLA and adverse outcome (Supplemental Table E2) [12]. Most patients with SLA had a decrease of serum lactate and increase of bicarbonate and pH during the 24-hour study period. Importantly, in this sub-cohort of patients with SLA, initial lactate concentration could not differentiate between survivors and no-survivors. Therefore, lactate concentration may not be a useful parameter for selecting AKI patients with SLA, who may benefit of treatment with RRT. Furthermore, RRT modality had no impact on outcome. Despite the severity of illness, short-term survival was reasonable with almost three quarters of the patients surviving for the first 24-hour period.

The strength of the study is that more than a decade after the most recent cohort study [21], it provides detailed and actualized data on a frequent used indication for initiation of RRT. Therefore, this study updates the previous report in a more contemporary population, submitted to the therapeutic modalities that are currently standard.

The prevalence of SLA at time of initiation of RRT is not well established in literature [24]. We found that this was a common finding in our study population, as one-third of ICU patients started on RRT had SLA. Retrospective determination of the cause and type of SLA is difficult, but given the fact that only 9.1% of patients were diagnosed with liver disease on admission, the majority of patients probably could be classified as type A lactic acidosis. Because of the single-center design of this study one has to be cautious in extrapolating these findings, especially, because the incidence found may even be an underestimation as we cannot rule out that some patients with SLA were not initiated on RRT, because of limitations in therapy.

The association between lactic acidosis and mortality was confirmed in this specific cohort of ICU patients. This may be explained by SLA itself, but the increased mortality may also be the consequence of greater severity of illness and organ dysfunction, of which the lactic acidosis is the consequence [6, 7].

This high mortality rate is comparable with previously reported data in ICU patients who had AKI and SLA [21, 25]. Despite advances in ICU patient management, mortality of this specific cohort has therefore not improved during the past decade. Alternatively, we cannot rule out that this comparison is affected by selection bias. Possibly, severely ill patients with important comorbidity who were not treated with RRT in the past may now have been allocated to RRT. Initiation of RRT in ICU patients with AKI and SLA is still a matter of debate. It may be seen as futile as the mortality is so high, and given the fact that the role of extracorporeal lactate clearance by RRT remains unclear. This study cannot give a clear answer at this point. RRT does not treat the underlying cause of lactic acidosis, which is essential in these patients. As such, it can only provide restoration of homeostatic equilibrium, enabling specific therapeutic measures [15].

During the study period, we found an improvement of acidosis parameters, and observed a 24-hour mortality that was less than 1 of 3 patients. These observations may be of some importance as prolonged duration of SLA for 24 hours or longer is strongly associated with mortality in diverse cohorts of ICU patients [11, 12]. In addition, even moderate increases in serum lactate concentration have been found to be associated with increased mortality [26]. As we did not measure lactate clearance by RRT, it is uncertain whether the effects we observed are explained by enhanced clearance of lactate, or are just the resultant of the natural course of disease. In addition, removal of other small anions such as isocitrate, malate and α-ketoglutarate, administration of bicarbonate by means of RRT; or a combination of both could have contributed to the observed clinical course.

Table 1.

Characteristics of AKI patients treated with RRT: comparison between patients without and with severe lactic acidosis.

IRRT indicates intermittent renal replacement therapy. Data in bold are statistically significant.

	TOTAL COHORT AKI-RRT	NO SLA	SLA	P
N	342	226 (66,1%)	116 (33,9%)	
DEMOGRAPHIC DATA				
Age (year)	65 (55,73)	65 (55,73)	65 (53,72)	0.349
Male gender	226 (66.1%)	157 (69.5%)	74 (64.0%)	0.289
APACHE II	21 (16,27)	20 (16,24)	24 (18,30)	**<0.001**
CHRONIC COMORBIDITY				
Cardiovascular disease	149 (43.6%)	117 (51.8%)	32 (27.6%)	**<0.001**
Diabetes mellitus	80 (23.4%)	56 (24.8%)	24 (20.7%)	0.398
TYPE OF ICU				
Medical ICU	104 (30.4%)	82 (36.3%)	22 (18.9%)	**<0.001**
Surgical ICU	153 (44.7%)	82 (36.3%)	71 (61.2%)	
Cardiac surgical ICU	80 (23.4%)	62 (27.4%)	18 (15.5%)	
Burn unit	5 (1.5%)	0 (0.0%)	5 (4.3%)	
ADMISSION CATEGORY				
Cardiovascular disease	97 (42.9%)	34 (29.3%)	131 (38.3%)	**0.012**
Respiratory disease	13 (5.8%)	4 (3.4%)	17 (5.0%)	
Gastrointestinal disease	14 (6.2%)	6 (5.2%)	20 (5.8%)	
Liver disease	16 (7.1%)	15 (12.9%)	31 (9.1%)	
Kidney disease	17 (7.5%)	1 (0.9%)	18 (5.3%)	
Hematologic disease	7 (3.1%)	5 (4.3%)	12 (3.5%)	
Sepsis/infection	30 (13.3%)	20 (17.2%)	50 (24.6%)	
Trauma/burn	11 (4.9%)	10 (8.6%)	13 (6.1%)	
Other	20 (8.8%)	21 (18.1%)	41 (12.1%)	
PARAMETERS AT TIME OF INITIATION OF RRT				
LOS ICU before RRT (days)	2.0 (1.1,3.9)	2.1 (1.4,3.1)	1.6 (0.4,4.4)	**0.015**
Serum creatinine (mg/dL)	3.67 (2.42,4.91)	2.83 (1.74,3.52)	4.58 (3.15,5.42)	**<0.001**
Serum urea (g/dL)	1.51 (1.14,2.13)	1.32 (0.87,1.92)	0.91 (0.61,1.24)	**<0.001**
Bilirubin	1.26 (0.50,2.70)	1.54 (0.30,3.42)	1.90 (0.99,4.70)	**0.001**
Thrombocytes (×10E9/L)	127.0 (79.8,202.0)	113.0 (65.0,183.0)	77.5 (46.3,138.0)	**<0.001**
pH	7.27 (7.19,7.33)	7.26 (7.18,7.33)	7.23 (7.12,7.33)	0.088
RRT MODALITY				
CVVHD	88 (25.7%)	28 (12.4%)	60 (51.7%)	**<0.001**
CVVH	55 (16.1%)	26 (11.5%)	29 (25.0%)	
IRRT	167 (48.8%)	151 (66.8%)	16 (13.8%)	
SLEDD	32 (9.4%)	21 (9.3%)	11 (9.5%)	
Continuous RRT modality	143 (41.8%)	54 (23.9%)	89 (76.7%)	**<0.001**
COMORBIDITY AT INITIATION OF RRT				
Mechanical ventilation	225 (65.8%)	129 (57.1%)	96 (82.8%)	**<0.001**
Vasoactive therapy	238 (69.6%)	139 (61.5%)	99 (85.3%)	**<0.001**
OUTCOMES				
LOS hospital (days)	28.5 (15.0,58.3)	24.2 (10.0,49.0)	12.3 (4.7,39.2)	**<0.001**
LOS ICU (days)	18.0 (8.0,35.0)	14.0 (6.0,32.2)	6.3 (2.9,24.3)	**<0.001**
ICU mortality	204 (59.6%)	107 (47.3%)	97 (83.6%)	**<0.001**
Hospital mortality	205 (59.9%)	108 (47.8%)	97 (83.6%)	**<0.001**

Table 2.

Patients with severe lactic acidosis: survivors versus non-survivors.

	SEVERE LACTIC ACIDOSIS	ICU SURVIVORS	ICU NONSURVIVORS	P
N	116	19 (16.4%)	97 (83.6%)	
DEMOGRAPHIC DATA				
Age (year)	65 (53,72)	52 (35.67)	65 (55.73)	**0.005**
Male gender	74 (64%)	9 (47.4%)	65 (67.0%)	0.103
APACHE II	24 (18,30)	20 (16.27)	25 (19.31)	0.066
CHRONIC COMORBIDITY				
Cardiovascular disease	32 (27.6%)	8 (42.1%)	24 (24.7%)	0.122
Diabetes mellitus	24 (20.7%)	2 (10.5%)	22 (22.7%)	0.232
TYPE OF ICU				
Medical ICU	22 (18.9%)	2 (10.5%)	20 (20.6%)	0.382
Surgical ICU	71 (61.2%)	13 (68.4%)	58 (59.8%)	
Cardiac surgical	18 (15.5%)	2 (10.5%)	16 (16.5%)	
Burn unit	5 (4.3%)	2 (10.5%)	3 (3.1%)	
ADMISSION CATEGORY				
Cardiovascular disease	34 (29.3%)	4 (21.1%)	30 (30.9%)	0.359
Respiratory disease	4 (3.4%)	0 (0.0%)	4 (4.1%)	
Gastrointestinal disease	6 (5.2%)	3 (15.8%)	3 (3.3%)	
Liver disease	15 (12.9%)	3 (15.8%)	12 (12.4%)	
Kidney disease	1 (0.9%)	0 (0.0%)	1 (1.0%)	
Hematologic disease	5 (4.3%)	0 (0.0%)	5 (5.2%)	
Sepsis/infection	20 (17.2%)	3 (15.8%)	17 (17.5%)	
Trauma/burn	10 (8.6%)	3 (15.8%)	7 (7.3%)	
Other	21 (20.2%)	3 (15.8%)	18 (18.1%)	
PARAMETERS AT TIME OF INITIATION OF RRT				
LOS ICU before RRT (days)	2.1 (1.4,3.1)	1.8 (1.3,2.6)	2.2 (1.5,3.2)	0.237
Serum lactate (mmol/L)	11.1 (7.3,17.9)	10.4 (7.8;18.0)	11.7 (7.3,17.9)	0.976
Serum creatinine (mg/dL)	2.50 (1.70,3.54)	1.93 (1.27,2.92)	2.60 (1.75,3.61)	**0.014**
Serum urea (g/dL)	0.91 (0.61,1.24)	0.58 (0.47,0.95)	0.93 (0.67,1.34)	**0.004**
Bilirubin (mg/dL)	1.90 (0.99,4.70)	2.15 (0.64,4.15)	1.90 (1.05,4.85)	0.446
Thrombocytes (×10E9/L)	77.5 (46.3,138.0)	71.0 (48.0,167.0)	78.0 (42.0,134.0)	0.460
pH	7.23 (7.12,7.33)	7.28 (7.21,7.33)	7.22 (7.08,7.33)	0.085
RRT MODALITY				
CVVHD	60 (51.7%)	12 (63.2%)	48 (49.5%)	0.607
CVVH	29 (25.0%)	3 (15.8%)	26 (26.8%)	
IRRT	16 (13.8%)	3 (15.8%)	13 (13.4%)	
SLEDD	11 (9.5%)	1 (5.3%)	10 (10.3%)	
Continuous RRT modality	89 (76.7%)	15 (79.0%)	74 (76.3%)	0.802
COMORBIDITY AT INITIATION OF RRT				
Mechanical ventilation	96 (82.8%)	16 (84.2%)	80 (82.5%)	0.855
Vasoactive therapy	99 (85.3%)	15 (78.9%)	84 (86.6%)	0.389

Data on lactate clearance by RRT are scarce and conflicting. Several researchers suggest only a limited therapeutic effect and state that increased lactate clearance may be the reflection of the improvement of the clinical situation rather than the removal of large amounts of lactate. These data are derived from studies employing lower dose of RRT than the ones prescribed routinely in our units [21, 27]. For example, Levraut et al found that with a relatively low dose of RRT (Continuous Veno-Venous HemoDiaFiltration with a Qb of 100 mL/min and Qd of 1000mL/h), RRT constituted only 3% of the total body clearance of lactate [28]. Interestingly, Bellomo [29] calculated that a Qb of 200 mL/min, lactate clearance during dialysis would reach approximately 20% of endogenous clearance.

Despite this conflicting literature, RRT is often used as a strategy in correcting severe acidosis as it may act as a bridging therapy that buys time to treat the underlying cause of the acidosis [30]. The finding that the initial lactate concentration was not related to mortality in this cohort of patients could be of interest to physicians attending patients with SLA and AKI. It suggests that lactate concentration may not be a useful parameter for selecting AKI patients with SLA, who will benefit of treatment with RRT. Also, no difference in mortality between RRT modalities was observed. This may be subject to selection bias given that the cohorts were small and not entirely comparable.

This study has some limitations. This is a retrospective single-center study with a relatively limited number of patients, which may limit external validity of the findings. Some data were missing due the gradual introduction of the electronic PDMS. In some patients we missed lactate concentrations at 4 or 24 hours after initiation of RRT. However, a sensitivity analysis demonstrated these had similar baseline characteristics and outcome compared to patients who had lactate concentrations measured. Therefore, it is unlikely that this impacted our findings. Further, only patients treated with RRT are studied. We do not have data on ICU patients who had AKI and SLA and who were not started on RRT. As such, we do not have data on the natural course of the disease. As we have the policy of using RRT as a bridging therapy that buys time to treat the underlying disorder, only incidental patients were missed for that reason. On the other hand, the condition of these patients was so severe, that the treating physician would have considered not initiating RRT unethical unless a decision to withdraw active treatment had been made. Therefore, we do not think there is clinical equipoise to perform a prospective randomized study on initiation of RRT in ICU patients with SLA and AKI. This situation is similar to many interventions in severely ill patients such as the initiation of mechanical ventilation.

In conclusion, prevalence of SLA in critically ill patients with AKI treated with RRT is high. During the first 24 hours of RRT, acidosis improved and lactate decreased in the majority of patients irrespective of RRT modality. Although nonsurvivors were more acidotic, lactate concentration at initiation of RRT was not able to discriminate between survivors and nonsurvivors in the cohort of patients with SLA at time of initiation of RRT. In AKI patients with SLA, lactate concentration at initiation of RRT may therefore not be a useful parameter for selecting those who will benefit of treatment with RRT.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. John Kellum and Dr. Lui Forni for their much valued comments that helped to improve the manuscript, Mr. Stefaan Claus and Mrs. Lilianne Geleyn for maintenance of the database, Mr. Christiaan Danneels for data retrieval from the ICU PDMS, and Dr Nadia Den Blauwen for data retrieval from the hospital administration ICD-9 database.

All authors have made material contributions to this manuscript according to the rules of authorship. WDC participated in data collection and analysis, and made the first draft of the paper. SV helped to design the study, and participated in data collection and analysis. JDW, AD, RV, and JDC helped to design the study and reviewed the first draft of the manuscript. EH had the original idea for the study, helped to design it, participated in analysis and revised the manuscript.

REFERENCES

[1] Mizock BA: Lactic acidosis. Disease-a-month : Dis Mon, 35(4), 1989, 233-300.

[2] Valenza F, Aletti G, Fossali T, Chevallard G, Sacconi F, Irace M, et al: Lactate as a marker of energy failure in critically ill patients: hypothesis. Crit Care, 9(6), 2005, 588-593.

[3] Kompanje EJ, Jansen TC, van der Hoven B, Bakker J: The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814-1869) in January 1843. Intensive Care Med , 33(11), 2007, 1967-1971.

[4] Kellum JA, Song M, Venkataraman R: Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. Chest , 125(1), 2004, 243-248.

[5] Marsh JD, Margolis TI, Kim D: Mechanism of diminished contractile response to catecholamines during acidosis. Am J Physiol , 254(1 Pt 2), 1988,H20-27.

[6] Clanachan AS: Contribution of protons to post-ischemic Na(+) and Ca(2+) overload and left ventricular mechanical dysfunction. Journal of cardiovascular electrophysiology, 17 Suppl 1, 2006, S141-S148.

[7] Wu D, Arias J, Bassuk J, Doods H, Seidler R, Adams JA, et al: Na+/H+ exchange inhibition delays the onset of hypovolemic circulatory shock in pigs. Shock, 29(4), 2008, 519-525.

[8] Crimi E, Taccone FS, Infante T, Scolletta S, Crudele V, Napoli C: Effects of intracellular acidosis on endothelial function: An overview. Journal of Critical Care, 27(2), 2012, 108-118.

[9] Leverve XM: Lactate in the intensive care unit: pyromaniac, sentinel or fireman? Crit Care, 9(6), 2005, 622-623.

[10] Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW: Etiology and therapeutic approach to elevated lactate levels. Mayo Clin Proc , 88(10), 2013, 1127-1140.

[11] McNelis J, Marini CP, Jurkiewicz A, Szomstein S, Simms HH, Ritter G, et al: Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. Am J Surg, 182(5), 2001, 481-485.

[12] Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC: Serum lactate and base deficit as predictors of mortality and morbidity. Am J Surg, 185(5), 2003, 485-491.

[13] Naka T, Bellomo R: Bench-to-bedside review: treating acid-base abnormalities in the intensive care unit--the role of renal replacement therapy. Crit Care, 8(2), 2004, 108-114.

[14] Colombi A, Tholen H: Haemodialysis in Treatment of Lactic Acidosis Associated with Acute Hepatic and Renal Failure. Postgrad Med J, 47(551), 1971, 628-31.

[15] Bellomo R, Lipcsey M, Calzavacca P, Haase M, Haase-Fielitz A, Licari E et al: Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis. Intensive Care Med, 39(3), 2013, 429-436.

[16] Cerda J, Tolwani AJ, Warnock DG: Critical care nephrology: management of acid-base disorders with CRRT. Kidney Int, 82(1), 2012, 9-18.

[17] Schetz M: Non-renal indications for continuous renal replacement therapy. Kidney Int, 56, 1999, S88-S94.

[18] Gibney N, Hoste E, Burdmann EA, Bunchman T, Kher V, Viswanathan R et al: Timing of initiation and discontinuation of renal replacement therapy in AKI: Unanswered key questions. Clin J Am Soc Nephro, 3(3), 2008, 876-880.

[19] KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney international Supplement, 2(1), 2012, 16-39.

[20] Forni LG, McKinnon W, Lord GA, Treacher DF, Peron JMR, Hilton PJ: Circulating anions usually associated with the Krebs cycle in patients with metabolic acidosis. Critical Care, 9(5), 2005,R591-R595.

[21] Hilton PJ, Taylor J, Forni LG, Treacher DF: Bicarbonate-based haemofiltration in the management of acute renal failure with lactic acidosis. Qjm-Mon J Assoc Phys, 91(4), 1998, 279-283.

[22] Reynvoet E, Vandijck DM, Blot SI, Dhondt AW, De Waele JJ, Claus S et al: Epidemiology of infection in critically ill patients with acute renal failure. Crit Care Med, 37(7), 2009, 2203-2209.

[23] Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. Crit Care Med, 13(10), 1985, 818-829.

[24] Gunnerson KJ, Kellum JA: Acid-base and electrolyte analysis in critically ill patients: are we ready for the new millennium? Curr Opin Crit Care, 9(6), 2003, 468-473.

[25] Mizock BA, Falk JL: Lactic-Acidosis in Critical Illness. Critical Care Medicine, 20(1), 1992, 80-93.

[26] Nichol A, Bailey M, Egi M, Pettila V, French C, Stachowski E et al: Dynamic lactate indices as predictors of outcome in critically ill patients. Crit Care, 15(5), 2011, R242.

[27] Briglia AE: The current state of nonuremic applications for extracorporeal blood purification. Semin Dial, 18(5), 2005,380-390.

[28] Levraut J, Ciebiera JP, Jambou P, Ichai C, Labib Y, Grimaud D: Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. Critical Care Medicine, 25(1), 1997, 58-62.

[29] Bellomo R: Bench-to-bedside review: Lactate and the kidney. Critical Care, 6(4), 2002, 322-326.

[30] Feriani M, Dell'Aquila R: Acid-base balance and replacement solutions in continuous renal replacement therapies. Kidney international Supplement, 66, 1998, S156-159.

Table E1.

Characteristics of treatment modalities.

Dialyzers used were low flux polyethersulfone (Diapes 1.6, Bellco) or high flux polysulfone hollow fibre cartridges (FX80 Fresenius).
CVVH | continuous veno-venous haemofiltration, **IHD** | intermittent haemodialysis, **CVVHD** | continuous veno-venous hemodialysis, **SLEDD** | slow extended daily dialysis

	DIFFUSIVE/ CONVECTIVE	DURATION	DIALYSIS MACHINE	BLOOD FLOW (QB) (ML/MIN)	DIALYSATE FLOW (QD) (ML/MIN)	EFFLUENT RATE (ML/HOUR)
CVVH	convective	continuous	Edwards Lifesciences, Accura			500 mL predilution 1500 mL postdilution
IHD	diffusive	4	Gambro AK200	150-200	500	
CVVHD	diffusive	continuous	Gambro AK200	100-200	350-500	
			Fresenius Genius	100-150	100-150	
SLEDD	diffusive	6-12	Gambro AK200	100-200	350	
			Fresenius Genius	100-200	100-200	

Table E2.

Impact of the presence of severe lactic acidosis therapy on mortality: multivariable logistic regression analysis.

Multivariate analysis adjusted for APACHE II, cardiovascular disease, mechanical ventilation, vasoactive therapy, type of ICU, RRT modality, serum bilirubin, serum thrombocyte count, serum urea, serum creatinine and pH at initiation of RRT
Goodness of fit according to Hosmer en Lemeshow | Chi2 = 3.328, df = 8, P = 0.912
RRT | Renal Replacement Therapy

	OR	95% CI	P
MODEL	Auc ROC: 0.812 (95% CI 0.757 - 0.866)		
SEVERE LACTIC ACIDOSIS (Compared to no severe lactic acidosis)	3.42	1.41 – 8.31	0.007

Table E3.

Patient characteristics in severe lactic acidosis patients with different evolution of serum lactate concentration over time.

ICU | Intensive Care Unit, RRT | Renal Replacement Therapy, MAP | Mean Arterial Pressure, LOS | Length of stay

	SEVERE LACTIC ACIDOSIS	SERUM LACTATE CONCENTRATION 4 HOURS AFTER TIME OF INITIATION OF RRT			SERUM LACTATE CONCENTRATION 24 HOURS AFTER TIME OF INITIATION OF RRT		
		STABILISATION OR DECREASE	INCREASE	P	STABILISATION OR DECREASE	INCREASE	P
N	116	69 (69.7 %)	30 (30.3 %)		63 (81.8 %)	14 (18.2 %)	
DEMOGRAPHIC DATA							
Age (year)	65 (53,72)	66.5 (55.0,74.7)	57.9 (48.4,67.3)	**0.028**	63.2 (49.9,72.9)	64.3 (55.3,68.1)	0.702
Male gender	74 (64.0%)	46 (66.7 %)	19 (63.3 %)	0.748	41 (65.1 %)	8 (57.1 %)	0.577
APACHE II	24 (18,30)	24.0 (20.3,30.0)	25.5 (17.8,31.0)	0.942	24 (19,31)	25 (20,29)	0.639
Liver cirrhosis	13 (11.2%)	6 (8.7 %)	5 (16.7 %)	0.246	6 (9.5 %)	3 (21.4 %)	0.210
TYPE OF ICU							
Surgical ICU	71(61.2%)	39 (81.3 %)	9 (18.8 %)	0.211	39 (81.3 %)	9 (18.8 %)	0.531
Medical ICU	22(18.9%)	12 (85.7 %)	2 (14.3 %)		12 (85.7 %)	2 (14.3 %)	
Cardiac Surgical ICU	18 (15.5%)	9 (90 %)	1 (10.0 %)		9 (90 %)	1 (10.0 %)	
Burn unit	5 (4.3%)	3 (60 %)	2 (40.0 %)		3 (60 %)	2 (40.0 %)	
PARAMETERS AT TIME OF INITIATION OF RRT							
Serum lactate (mmol/L)	11.1 (7.3,17.9)	12.2 (6.9,19.2)	10.6 (8.0,18.0)	0.846	11.8 (6.9,18.0)	9.1 (7.7,12.8)	0.227
Serum urea (g/dL)	0.91 (0.61,1.24)	0.92 (0.61,1.23)	0.88 (0.58,1.42)	0.879	0.90 (0.58,1.19)	0.90 (0.63,1.42)	**0.355**
Serum creatinine (mg/dL)	2.50 (1.70,3.54)	2.68 (1.74,3.69)	2.26 (1.63,3.42)	0.283	2.56 (1.59,3.46)	2.84 (1.88,4.95)	**0.338**
pH	7.23 (7.12,7.33)	7.30 (7.19,7.35)	7.16 (7.03,7.27)	**0.002**	7.27 (7.18,7.33)	7.26 (7.17,7.33)	0.202
HCO3- mmol/L	16.8 (13.6,21.3)	18.6 (14.5,22.9)	15.1 (8.9,18.1)	**<0.001**	18.0 (13.9,21.5)	15.3 (13.1,17.7)	0.774
Mechanical ventilation	96 (82.8 %)	53 (76.8 %)	29 (96.7%)	**0.016**	52 (82.5 %)	11 (78.6 %)	0.728
Vasopressor treatment	99 (85.3 %)	57 (82.6 %)	26 (86.7 %)	0.614	55 (87.3 %)	12 (85.7 %)	0.875
Blood pressure MAP (mm Hg)	64 (59,73)	64.0 (58.5,72.5)	65.0 (58.8,74.3)	0.546	66.0 (58.5,77.0)	62.5 (54.5,72.0)	0.238
Serum Bilirubin (mg/dL)	1.90 (0.99,4.70)	1.80 (1.10,4.50)	2.85 (0.93,11.90)	0.132	2.25 (1.00,4.48)	3.16 (1.19,19.76)	0.199
RRT MODALITY							
Continuous therapy (CHD, CVVH D)	89 (77.0%)	49 (71.0 %)	26 (86.7 %)	0.095	49 (77.8 %)	12 (85.7 %)	0.721
Haemodialysis (IHD,SLEDD,CVVHD)	87 (75.0%)	49 (71.0 %)	23 (76.7 %)	0.562	47 (74.6 %)	9 (64.3 %)	0.511
OUTCOME							
LOS ICU before initiation RRT (days)	2.1 (1.4,3.1)	2.2 (1.5,3.1)	2.1 (1.3,3.8)	0.681	2.1 (1.6,3.0)	1.9 (1.1,4.3)	0.383
LOS hospital before initiation RRT (days)	3.7 (2.0,10.3)	3.2 (2.1,9.6)	5.0 (1.9,13.3)	0.532	3.1 (2.0,9.0)	4.8 (2.7,15.9)	0.217
ICU Mortality	97 (83.6%)	59 (85.5%)	23 (76.7%)	0.284	48 (76.6%)	11 (76.9%)	0.978
Hospital Mortality	97 (83.6%)	59 (85.5%)	23 (76.7%)	0.284	48 (76.6%)	11 (76.9%)	0.978

Table E4.

Comparison of different RRT modalities in patients with severe lactic acidosis.

Diffusive therapy: continuous haemodialysis (CHD) and slow extended daily dialysis (SLEDD); Convective therapy: intermittent haemodialysis (IHD) and continuous veno-venous hemofiltration (CVVH); Continuous therapy: CHD and CVVH; Intermittent therapy: IHD/SLEDD. **ICU** | Intensive Care Unit, **RRT** | Renal Replacement Therapy, **MAP** | Mean Arterial Pressure, **LOS** | Length of stay

	DIFFUSIVE RRT	CONVECTIVE RRT	P	INTERMITTENT /HYBRID RRT	CONTINUOUS RRT	P
N	87 (75.0%)	29 (25.0%)		27 (23.3%)	89 (76.7%)	
DEMOGRAPHIC DATA						
Age (year)	66 (53,72)	63 (51,74)	0.816	**65 (53,72)**	65 (53,72)	0.806
Male gender	55 (63.2 %)	19 (65.5 %)	0.823	19 (70.4 %)	55 (61.8 %)	0.417
APACHE II	25 (20,32)	23 (17,28)	0.067	25 (17,29)	25 (19,32)	0.325
Liver cirrhosis	8 (9.2 %)	5 (17.2 %)	0.306	2 (7.4 %)	11 (12.4 %)	0.730
TYPE OF ICU						
Surgical ICU	58 (81.7 %)	13 (18.3 %)	<0.001	18 (74.6 %)	53 (25.4 %)	0.912
Medical ICU	20 (90.9 %)	2 (9.1 %)		4 (18.2 %)	18 (81.8 %)	
Cardiac Surgical ICU	7 (39.9 %)	11 (61.1 %)		4 (22.2 %)	14 (77.8 %)	
Burn unit	2 (40.0 %)	3 (60.0 %)		1 (20.0 %)	4 (80.0 %)	
PARAMETERS AT TIME OF INITIATION OF RRT						
Serum Lactate (mmol/L)	11.8 (7.7,18.1)	10.1 (6.5,16.2)	0.215	7.7 (6.1,13.2)	12.5 (8.0,18.8)	**0.006**
Serum Urea (g/dL)	0.84 (0.59,1.22)	1.07 (0.71,1.40)	0.098	0.84 (0.63,1.32)	0.91 (0.60,1.23)	0.634
Serum Creatinine (mg/dL)	2.12 (1.58,3.28)	3.50 (2.28,4.72)	0.001	2.11 (1.97,3.40)	2.58 (1.59,3.61)	0.670
Acidosis (pH < 7.35)	74 (85.1 %)	21 (72.4 %)	0.126	18 (66.7 %)	77 (86.5 %)	**0.042**
pH	7.22 (7.08,7.33)	7.30 (7.19,7.37)	0.053	7.32 (7.24,7.39)	7.20 (7.10,7.33)	**0.002**
HCO_3- mmol/L	15.4 (12.7,21.0)	18.8 (15.4,21.5)	**0.044**	18.6 (14.2,23.8)	15.5 (13.5,20.8)	**0.038**
Mechanical ventilation	72 (82.8 %)	24 (82.8 %)	1.000	21 (77.8 %)	75 (84.3 %)	0.561
Vasopressor need	76 (87.4 %)	23 (79.3 %)	0.363	22 (81.5 %)	77 (86.5 %)	0.540
Blood pressure MAP (mm Hg)	64 (59,73)	63 (60,74)	0.659	69 (61,76)	63 (58,73)	0.073
Serum Bilirubin (mg/dL)	1.8 (0.9,4.4)	2.60 (1.20,5.13)	0.154	1.57 (0.65,2.13)	2.19 (1.13,5.00)	**0.038**
OUTCOME						
LOS ICU before initiation RRT (days)	6.1 (2.8,22.2)	7.0 (3.8,32.6)	0.245	5.7 (2.6,20.1)	6.4 (3.2,24.6)	0.601
LOS hospital before initiation RRT (days)	12.3 (4.0,39.2)	10.5 (6.8,38.4)	0.659	11.8 (4.0,31.3)	12.4 (5.1,42.5)	0.353
24 hour Mortality	26 (29.9%)	7 (24.1%)	0.552	7 (27.0%)	30 (33.3%)	0.571
ICU Mortality	71 (81.6%)	26 (89.7%)	0.311	23 (85.2%)	74 (83.1%)	0.802
Hospital Mortality	71 (81.6%)	26 (89.7%)	0.311	23 (85.2%)	74 (83.1%)	0.802

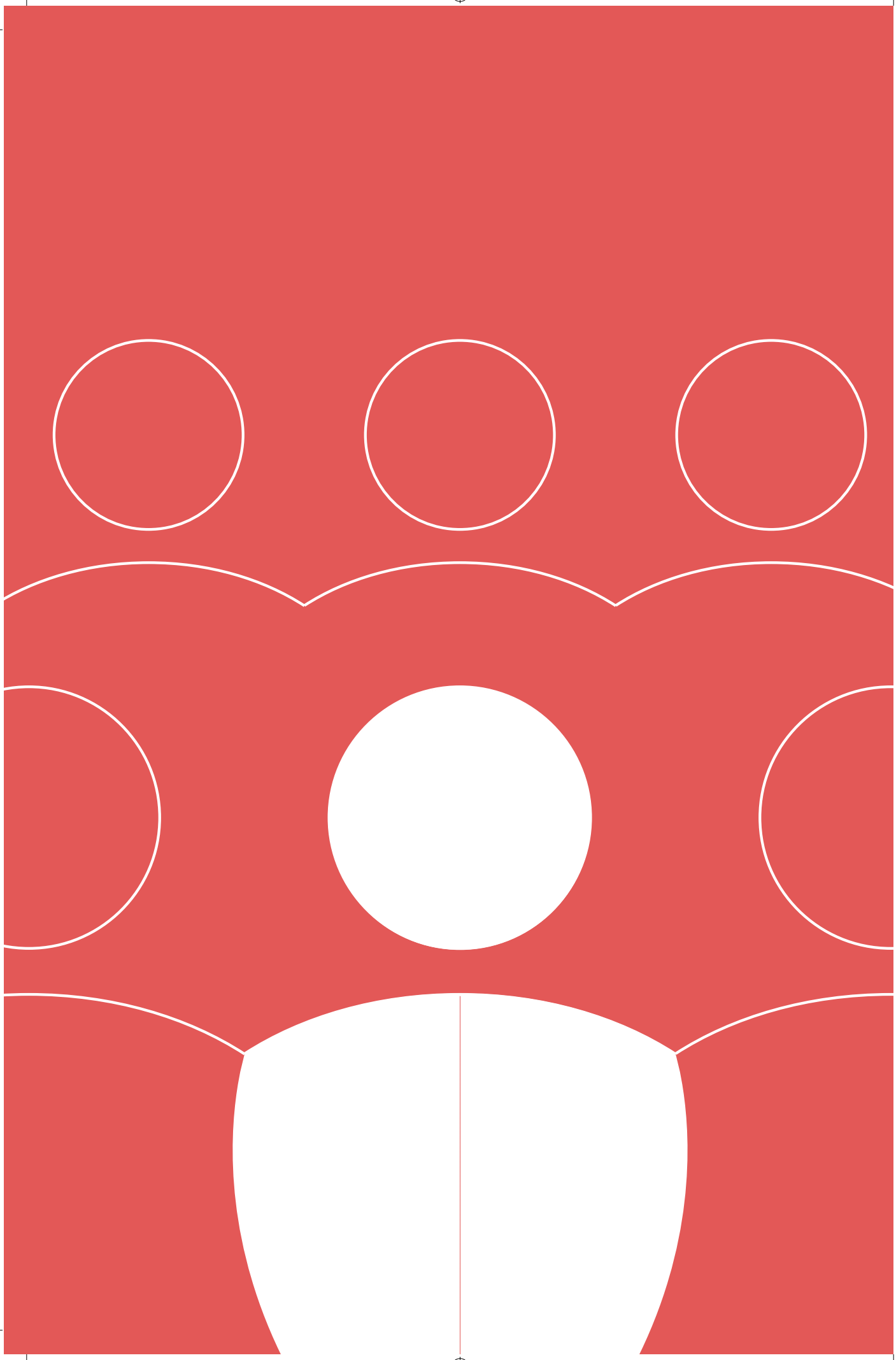
Table E5.

Impact of modality of renal replacement therapy on mortality: multivariable logistic regression analysis.

Multivariate analysis adjusted for age, gender, APACHE II, pH, serum creatinine, serum urea, cardiovascular disease.

Model 1 | Hosmer en Lemeshow 'goodness of fit' Chi2 = 5.811, df = 8, P = 0.661
Model 2 | Hosmer en Lemeshow 'goodness of fit' Chi2 = 3.153, df = 8, P = 0.924
Model 3 | Hosmer en Lemeshow 'goodness of fit' Chi2 = 3.423, df = 8, P = 0.905
RRT | Renal Replacement Therapy

	OR	95% CI	P
MODEL 1	Auc ROC: 0.667 (0.544 – 0.789)		
Continuous RRT (compared to intermittent RRT)	0.27	0.04 – 1.65	0.156
MODEL 2	Auc ROC : 0.715 (0.597 – 0.833)		
Diffusive RRT (compared to convective RRT)	0.59	0.12 – 2.93	0.518
MODEL 3	Auc ROC : 0.686 (0.564 – 0.808)		
Continuous RRT (compared to intermittent RRT)	0.20	0.03 – 1.30	0.092
Diffusive RRT (compared to convective RRT)	0.37	0.06 – 2.11	0.262



5

Long-term outcome in ICU patients with acute kidney injury treated with renal replacement therapy: a prospective cohort study.

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PUBLISHED IN
Crit Care. 2016
Aug 12;20(1):256.

BACKGROUND

In ICU patients, acute kidney injury treated with renal replacement therapy (AKI-RRT) is associated with adverse outcomes. The aim of this study was to evaluate variables associated with long-term survival and kidney outcome and to assess the composite endpoint major adverse kidney events (MAKE; defined as death, incomplete kidney recovery, or development of end-stage renal disease treated with RRT) in a cohort of ICU patients with AKI-RRT.

METHODS

We conducted a single center prospective observational study in a 50-bed ICU tertiary care hospital. During the study period from August 2004 through December 2012, all consecutive adult patients with AKI-RRT were included. Data were prospectively recorded during the patients' hospital stay and were retrieved from the hospital databases. Data on long-term follow-up were gathered during follow-up consultation or, in absence of this by consulting the general physician.

RESULTS

AKI-RRT was reported in 1,292 out of 23,665 first ICU admissions (5.5%). Mortality increased from 59.7% at hospital discharge, to 72.1% at 3 years. A cox proportional hazard model demonstrated association of increasing age, severity of illness, and continuous RRT with long-term mortality. Among hospital survivors with reference creatinine measurements, 1-year renal recovery was complete in 48.4% and incomplete in 32.6%. Dialysis dependency was reported in 19.0% and associated with age, diabetes, CKD and oliguria at time of initiation of RRT. MAKE increased from 83.1% at hospital discharge to 93.7% at 3 years. Multivariate regression analysis showed no association of classical determinants of outcome (preexisting CKD, timing of iniation of RRT and RRT modality with MAKE at 1 year.

CONCLUSION

Our study demonstrates poor long-term survival after AKI-RRT that was determined mainly by severity of illness and RRT modality at iniation of RRT. Renal recovery is limited, especially in patients with acute-on-chronic kidney disease, making nephrological follow-up imperative. MAKE is mainly associated with variables determining mortality.

1. Background

AKI is a frequent finding in ICU patients, with a prevalence of approximately 40-57% when defined according to the KDIGO criteria. AKI treated with renal replacement therapy (AKI-RRT) occurs in approximately 13% of ICU patients [1, 2]. It is associated with adverse outcomes such as increased length-of-stay, short- and long-term mortality and ESRD. In the past, AKI was considered a surrogate marker marker for severity of illness, and patient mortality was considered a consequence of the underlying disease [3]. However, there is an abundance of epidemiologic data that demonstrates that AKI in itself leads to adverse outcome. This is so for the most severe form of AKI, where patients are treated with RRT [4, 5]. In addition, small decreases in kidney function are associated with increased short-term mortality. Further, the prevalence of preexisting CKD is increasing amongst ICU admissions. CKD may lower the threshold for developing AKI, and acute-on-chronic kidney disease is associated with adverse outcomes [3-7]. Further, even mild AKI may predispose patients to CKD and so increases the risk of subsequent AKI events and finally ESRD [8-10]. So, AKI can be considered both the cause and consequence of CKD, and AKI and CKD therefore are considered interconnected and integrated syndromes [6]. The association of CKD with mortality remains a matter of debate. One one hand, a recent large registry study demonstrated the association with CKD and death [7]. On the other hand, critically ill patients with AKI-RRT, who had CKD were reported to have lower short-term mortality compared to those without preexisting CKD [9, 11-14]. Another factor that may impact on long-term outcomes is modality of RRT. Observational studies suggest that CRRT is associated with better kidney outcomes, more specifically less need for chronic dialysis [8, 9]. However, prospective randomized studies could not demonstrate a survival benefit for CRRT compared to intermittent therapies [10, 11]. Finally, optimal timing of initiation of RRT is unclear. RRT is initiated early in the absence of serious complications of AKI and may therefore have some advantages.

⟶ KEY MESSAGE

Long-term survival and renal recovery after AKI-RRT in critically ill patients is poor making nephrological follow-up imperative.

The late and more conservative approach takes into account that some patients with severe AKI might recover kidney function spontaneously without starting RRT, avoiding adverse events linked to RRT [12].

Until recently, studies of AKI in ICU patients were focused on conventionally accepted short-term outcomes such as mortality at day 30, or ICU and hospital discharge. However, these endpoints may underestimate the true burden of kidney disease. In light of the increasing focus on long-term outcomes, researchers in several studies have investigated the links between AKI, CKD and ESRD [13, 14]. By way of analogy to major adverse cardiovascular events, this led to the introduction of the composite endpoint MAKE [15]. MAKE is a composite of death, ESRD needing dialysis and incomplete kidney recovery, defined as a 25% decrease of eGFR, measured at long-term endpoints such as 90 days or 1 year.

The aim of the present study was to describe long-term patient and kidney outcomes in a cohort of AKI-RRT patients and to assess possible modifying factors of outcome, such as CKD, timing of initiation of RRT and RRT modality .

2. Methods

We conducted a single center prospective cohort analysis of patients with AKI-RRT at the ICU of the Ghent University Hospital over an 8-year study period (October 2004 – October 2012). The Ghent University ICU consists of a 22 beds surgical ICU, a 14 beds medical ICU, an 8 beds cardiac surgery ICU, and a 6 beds burn unit.

2.1 STUDY COHORT

The inclusion criteria were ICU patients aged ≥ 15 years, who had AKI and were treated with RRT and who had follow-up data after hospital discharge. During the study period, the electronic PDMS was gradually introduced. Only patients who were registered in the PDMS were included in the study [16]. Exclusion criteria were extracorporeal blood purification techniques for reasons other than AKI, patients with CKD receiving chronic RRT, RRT initiated before the admission to the ICU, and RRT immediately after kidney transplant. In cases were a patient had several ICU episodes of AKI-RRT during the same hospital admission, we considered only the first episode.

Indications for RRT, as well as the modality chosen (i.e. intermittent hemodialysis (IHD) (duration 2 to 4 h per treatment session), SLEDD (duration 6 to 12 h per treatment session), or continuous renal replacement therapy (CRRT) (continuous veno-venous hemofiltration or –hemodialysis)), were determined by consensus between the attending intensivists and nephrologists and based on the clinical status of the patient (fluid balance, respiratory status, acid-base balance). Continuous modalities are preferentially used in patients with severe shock, patients who are at risk for cerebral oedema (e.g. liver cirrhosis) or patients from whom fluid removal is pursued [17].

3. Definitions

Reference serum creatinine was either a baseline serum creatinine concentration obtained from the laboratory database within a 12-month period prior to hospital admission or, if unavailable, serum creatinine at time of hospital admission. In the latter group, some patients already had AKI at time of hospital admission. Therefore, in the group for which we had to rely on hospital admission creatinines, we excluded patients who were initiated on RRT within 2 days after hospital admission, as well as patients who had a higher serum creatinine concentration at the time of admission than at to hospital discharge. We did not apply back-calculation of baseline serum creatinine with the MDRD eGFR formula as suggested by the KDIGO AKI guidelines, because this would have led to underestimation of the number of patients with preexisting CKD stage 3 or higher [18].

Timing of initiation of RRT was defined using the KDIGO staging criteria. Initiation of RRT at KDIGO stage 1 or 2 was defined as “early”, and initiation of RRT at stage 3 was defined as “late”. Oliguria was defined as a diuresis of less than 500 mL over 24h preceding the

initiation of RRT. Fluid balance comprising the 24h episode before initiaton of RRT was calculated by the PDMS. Recovery of kidney function was assessed only in patients with reference creatinine. Recovery of kidney function was classified as complete when eGFR was within 25% from reference eGFR (based on reference serum creatinine). Incomplete kidney recovery comprised patients who had a 25% or greater decline of reference eGFR and who were not treated with dialysis. Absent kidney recovery was defined as the permanent need for RRT for more than 3 months. Since long-term serum creatinine data were available at the exact follow up times (e.g. 90days) we allowed the following intervals: day 90 ± 7 days, 1 year ± 60 days, 2 year ± 60 days, 3 years ± 60 days.

CKD was defined according to eGFR categories per the KDIGO criteria [19]: Stage 1 CKD is an eGFR > 90 ml/min/1.73 m², stage 2 is 60 – 90 ml/min/1.73 m², stage 3 is 30-60 ml/min/1.73 m², stage 4 is 15 – 30 ml/min/1.73 m², and stage 5 is <15 ml/min/1.73 m² or chronic RRT (hemodialysis or peritoneal dialysis). Patients with CKD stage 3 or worse were classified for the purposes of this study as patients with CKD and compared with patients who had CKD stage 2 or less (no CKD) [15]. Late initiation of RRT was defined as initiation of RRT at KDIGO stage 3. The MAKE composite endpoint was assessed in the patient cohort with reference creatinine, and it was defined as the presence of one or more of the following: death, incomplete kidney recovery, or development of ESRD treated with RRT [15].

4. Study outcomes

The primary outcome measure of the study was mortality 1 year after initiation of RRT. The secondary outcomes were long-term patient survival and long-term kidney function measured as kidney recovery and dialysis dependency in hospital survivors. In addition, we reported and evaluated the composite outcome measure MAKE. We eventually assessed the classical determinants of long-term outome of AKI treated with RRT: preexisting CKD, timing of initiation of RRT, and RRT modality.

4.1 DATA COLLECTION

Data were prospectively recorded during hospital stay. Baseline demographic parameters were retrieved from the hospital's electronic database and the ICU's electronic PDMS. Data on comorbidity and diagnostic categories were retrieved from the electronic hospital administration's International Classification of Diseases, Ninth Revision, coding system. The severity of illness as determined by the (SAPS II score (based on data recorded during the first 24-hours of ICU admission) was recorded at the time of ICU admission [20, 21]. At the time of initiation of RRT, severity of illness was assessed on the basis of parameters of organ dysfunction and SOFA score [22]. Kidney laboratory data were recorded at hospital admission; ICU admission; initiation of RRT; hospital discharge; and 30 and 90 days and 1, 2 and 3 years. Data on long-term follow-up were gathered from the patients' electronic medical records (e.g. during follow-up consultation, or in cases of absence of such a consultation, by contacting the primary care physician of the patient by e-mail or telephone).

4.2 STATISTICAL ANALYSIS

The data are expressed as number (proportion), median (interquartile range), or OR (95% CI). Univariate analysis of long-term mortality and MAKE were performed with the Mann-Whitney U test, Fisher's exact test, Friedman's two-way analysis of variance by ranks test, Wilcoxon rank-sum test, Kruskall Wallis test and chi-square test, as appropriate. The predictors thus obtained were subsequently tested in a multivariable logistic regression model. Variables selected for inclusion in the regression model were those with plausible rationale, with a P value ≤0.25 in bivariate analysis. Significant covariates for MAKE were identified after constructing a model in which all covariates were entered simultaneously (enter method). We analyzed for colinearity by assessing correlations between covariates; in addition, interaction was explored. Goodness of fit was assessed according the method described by Hosmer and Lemeshow. Statistical significance was accepted when the P value was <0.05.

Fig. 1.

Study flowchart

PDMS | patient data management system, AKI | acute kidney injury, ICU | intensive care unit, RRT | renal replacement therapy

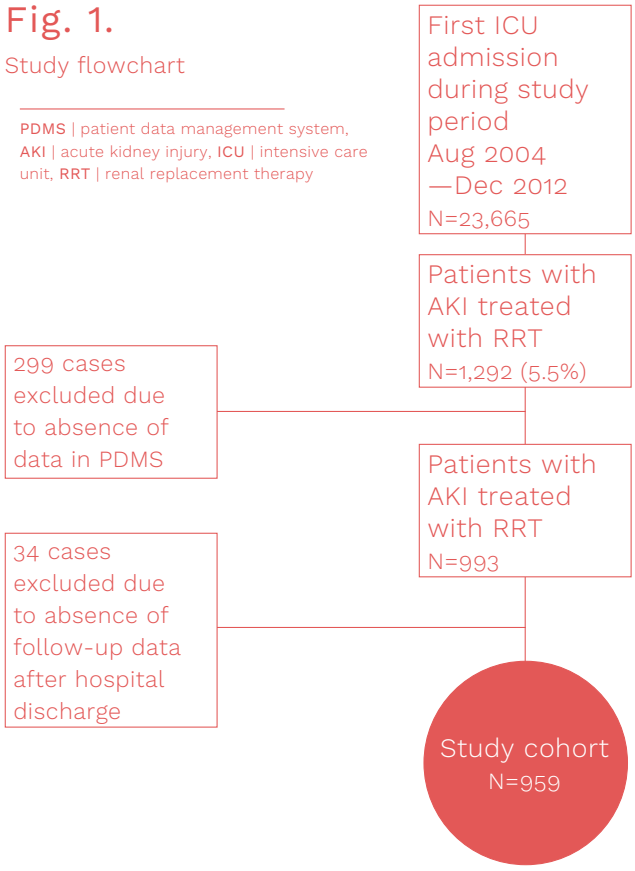
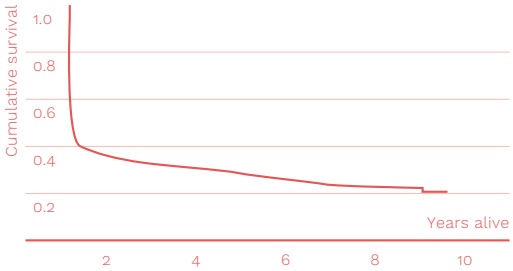


Fig. 2.

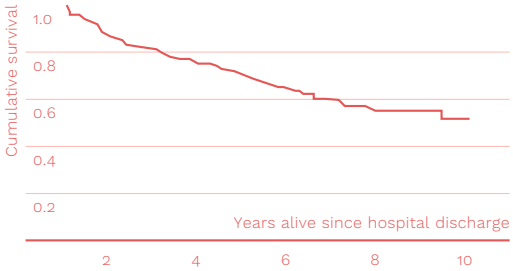
Kaplan-Meier survival curve

IHD | Intermittent Hemodialysis, SLEDD | Slow Extended Daily Dialysis, CRRT | Continuous Renal Replacement Therapy

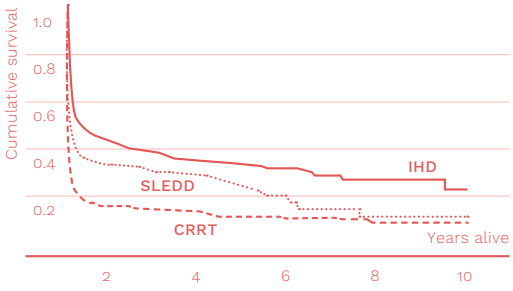
a. Kaplan-Meier survival curve over time for the whole cohort.



b. Kaplan-Meier survival curve over time in hospital survivors.



c. Kaplan-Meier survival curve stratified for RRT modality (log rank P<0.001).



The event-free survival rate was estimated using the Kaplan-Meier method, and significance was evaluated with the log-rank test. A Cox proportional hazards model was developed to address the predictors for long-term survival. These analyses were performed with use of IBM SPSS Statistics for Windows, version 23.0.0 (IBM, Armonk, NY, USA).

5. Results

During the 8-year study period, 23,665 first ICU admissions were registered. A total of 1,292 patients (5.5%) had AKI-RRT, and 959 patients were included in the final analyses **(Fig. 1)**. Of these, 609 patients (63.4%) had a reference creatinine level documented. Demographic data of the study cohort are shown in **Table 1.**

5.1 PATIENT OUTCOME AND LONG-TERM SURVIVAL

ICU mortality was 54.6%. Mortality increased from 59.7% at time of hospital discharge, to 64.5% at 1 year, 67.9% at 2 years and 72.1% at 3 years **(Fig. 2a)**. Among hospital survivors, 11.9% later died at 1 year, 19.3% at 2 years and 27.2% at 3 years **(Fig. 2b)**.

One-year nonsurvivors were significantly older than survivors but had less CKD. A greater proportion of nonsurvivors were female and had been admitted to the medical ICU. At ICU admission, nonsurvivors' severity of illness based on their SAPS II scores were higher than those of survivors. At initiation of RRT, nonsurvivors had higher SOFA scores than survivors. Their hemodynamic status was more unstable as a greater proportion of patients was treated with vasoactive agents, had a positive fluid balance, were more acidotic, and had higher serum lactate and more negative base excess. Nonsurvivors were less often treated with diuretics, and a greater proportion were mechanically ventilated and treated with CRRT as the initial RRT modality **(Table 1)**. Patients treated with CRRT as initial RRT modality had worse survival than patients treated with IHD (P<0.001 by log-rank test) **(Fig. 2c)**.

We found that, after adjustment for confounders in a Cox proportional hazards model, CRRT as initial RRT modality was associated with long-term mortality (HR 1.570; 95% CI 1.202,2.050; P=0.001). Baseline kidney function and timing of RRT were not associated with survival in this model. Other confounders associated with survival were older age, and increased severity of illness (full model provided in **Additional file 1: Table S1**).

5.2 KIDNEY OUTCOMES

Nephrology consultation after hospital discharge was reported in only 34.0% of hospital survivors. Nephrology follow-up was more frequent in CKD stage ≥3 patients compared with CKD stage <3 patients (51.0% versus 31.8%, P=0.003). Among hospital survivors dialysis dependency rates were 8.6% at hospital discharge, 9.0% at 90 days, 14.1% at 1 year, 14.0% at 2 year and 16.9% at 3 year.

In order to assess kidney outcomes with focus on (in)complete renal recovery, the cohort of hospital survivors who had a reference creatinine was studied **(Table 2)**. In these patients we found that after 1-y follow up 48.4% had complete recovery of kidney function, 32.6% had incomplete recovery, and 19.0% had ESRD and were treated with chronic dialysis. Patients who had incomplete recovery had better kidney function and less often diabetes before AKI. Patients receiving chronic dialysis more often had diabetes, CKD, and oliguria at time of initiation of RRT. The evolution of kidney outcome over time is summarized in **Figure 3**. Complete renal recovery peaked at 90 days (56.7%) and further decreased over time. Dialysis dependency increased over time with 13.8% at hospital discharge up to 28.1% at 3 years. Patients who had prior CKD had more ESRD treated with dialysis compared to patients without CKD, but less incomplete renal recovery (without need for RRT) **(Table 3)**.

5.3 MAJOR ADVERSE KIDNEY EVENTS (MAKE)

Over time, MAKE increased in the total cohort; it was present in 83.1% of the patients at hospital discharge, 86.0% at 90 days, 87.5% at one year and 92.4% and 93.7% at two and three years

Table 1.

Patient demographics and comparisons.

Statistically significan tdata (P<0.05) are presented in bold.

CKD | Chronic Kidney Disease, CRRT | Continuous Renal Replacement Therapy, eGFR | estimated glomerular filtration ratio, ICU | intensive care unit, IHD | intermittent hemodialysis, KDIGO | Kidney Disease: Improving Global Outcomes, MAKE | major adverse kidney events, RRT | renal replacement therapy, SAPS II | Simplified Acute Physiology Score II, SLEDD | Slow Extended Daily Dialysis, SOFA | Sepsis-related Organ failure Assessment score. Data are presented as median (interquartile range) unless otherwise indicated.

	TOTAL COHORT	1 YEAR SURVIVORS	1 YEAR NON -SURVIVORS	P	MAKE 1 YR ABSENT	MAKE 1 YR PRESENT	P
N	959	340	619		102	752	
DEMOGRAPHIC DATA							
Age (year)	65 (55,75)	64 (52,74)	65 (55,75)	**0.030**	66 (57,74)	65 (55,75)	0.802
Gender (male, %)	65.4	70.0	62.8	**0.026**	64.6	64.0	0.892
Black (%)	0.2	0	0.3	0.294	0	0.3	0.593
COMORBID CONDITIONS							
Diabetes mellitus (%)	27.5	27.4	27.6	0.928	29.4	28.6	0.864
CKD stage baseline ≥ 3 (%)	39.6	44.2	37.0	0.084	51.6	37.3	**0.010**
eGFR baseline (mL/min/1.73 m²)	69.0 (47.0,91.1)	63.4 (44.4,82.9)	74.1 (49.2,93.8)	**0.004**	57.3 (42.8,76.5)	72.9 (49.2,93.4)	**0.001**
Serum Creatinine baseline (mg/dL)	1.07 (0.82,1.41)	1.15 (0.92,1.48)	1.00 (0.79,1.31)	**<0.001**	1.21 (0.96,1.58)	1.03 (0.80,1.34)	**<0.001**
CHARACTERISTICS ON ICU ADMISSION							
TYPE OF ICU							
Medical (%)	45.8	36.4	51.1	**<0.001**	32.0	49.6	**0.001**
Surgical (%)	54.2	63.6	48.9		68.0	50.4	
TIMING OF SURGERY							
Urgent (%)	61.0	60.2	61.8	0.729	60.2	61.8	0.012
Elective (%)	39.0	39.8	38.2		39.8	38.2	
SEVERITY OF ILLNESS							
SAPS II	63 (45,78)	52 (39,69)	70 (54,83)	**<0.001**	49 (34,69)	68 (49,82)	**<0.001**
CHARACTERISTICS AT INITIATION OF RRT							
SEVERITY OF ILLNESS							
SOFA total	10 (6,14)	9 (5,12)	12 (8,15)	**<0.001**	5 (1,9)	11 (7,14)	**<0.001**
SOFA non-renal	7 (3,11)	6 (2,9)	8 (5,12)	**<0.001**	8 (5,12)	8 (4,11)	**<0.001**
Mechanical ventilation (%)	88.6	82.4	92.0	**<0.001**	80.8	90.1	**0.006**
Vasoactive medication (%)	66.2	52.0	74.0	**<0.001**	48.0	70.4	**<0.001**
RENAL CHARACTERISTICS							
Oliguria (%)	48.9	45.8	50.8	0.171	36.6	50.9	**0.010**
Fluid balance (ml)	2163 (1180,3578)	2021 (1019,3220)	2200 (1268,4000)	**0.049**	1919 (1003,2996)	2229 (1311,4000)	0.054
Urine output (ml)	561 (178,1080)	621 (246,1230)	529 (157,1020)	0.055	792 (297,1483)	529 (152,1055)	**0.007**
Diuretics (%)	49.3	56.7	45.2	**0.001**	61.3	45.9	**<0.001**
ICU to RRT length-of-stay (days)	2 (1,7)	2 (1,5)	2 (1,8)	**0.050**	2 (1,6)	3 (1,8)	0.144
Serum creatinine (mg/dL)	3.57 (2.62,4.69)	4.23 (3.26,5.58)	3.26 (2.38,4.25)	**<0.001**	4.18 (3.11,5.14)	3.38 (2.47,4.44)	**<0.001**
LABORATORY PARAMETERS							
Serum Hemoglobin (g/dL)	9.3 (8.3,10.3)	9.5 (8.6,10.5)	9.2 (8.2,10.2)	**0.001**	9.4 (8.6,10.4)	9.2 (8.2,10.2)	**0.001**
Platelets (x 10^3/mm^3)	115 (67,184)	146 (89,219)	100 (55,158)	**<0.001**	144 (89,202)	104 (60,177)	**<0.001**
Serum Sodium (mmol/L)	139 (135,144)	138 (134,142)	140 (136,145)	**<0.001**	137 (133,142)	140 (136,144)	**<0.001**
Serum Potassium (mmol/L)	4.6 (4.1,5.3)	4.8 (4.2,5.4)	4.6 (4.1,5.2)	**0.012**	4.9 (4.2,5.4)	4.6 (4.1,5.2)	**0.007**
Serum Chloride (mmol/L)	102 (98,107)	101 (97,106)	103 (98,108)	0.051	101 (97,106)	103 (98,108)	**0.005**
Serum Bilirubin (mg/dL)	1.6 (0.7,4.2)	1.3 (0.6,3.3)	1.7 (0.7,4.8)	**0.004**	1.35 (0.60,2.90)	1.27 (0.86,1.82)	**0.001**
Serum Urea (g/dL)	1.28 (0.90,1.83)	1.33 (0.99,1.83)	1.26 (0.85,1.87)	0.062	1.36 (1.00,1.85)	1.27 (0.86,1.82)	0.173
Serum Albumin (g/dL)	2.2 (1.8,2.6)	2.3 (2.0,2.8)	2.1 (1.8,2.5)	**<0.001**	2.3 (2.0,2.6)	2.2 (1.8,2.6)	**0.003**
Lactate (mg/dL)	24 (12,82)	15 (10,36)	34 (15,100)	**<0.001**	14 (9,29)	29 (14,94)	**<0.001**
pH	7.30 (7.24,7.37)	7.34 (7.27,7.39)	7.29 (7.21,7.36)	**<0.001**	7.33 (7.27,7.38)	7.29 (7.22,7.36)	**<0.001**
Base Excess	-5.2 (-8.3,-2.2)	-4.2 (-6.4,-1.6)	-6.0 (-9.4,-2.5)	**<0.001**	-4.5 (-7.1,-1.8)	-5.5 (-9.1,-2.5)	**0.001**
RRT MODALITY							
IHD (%)	54.0	67.6	46.4	**<0.001**	72.5	49.5	**<0.001**
SLEDD (%)	15.8	16.2	15.6		14.7	15.5	
CRRT (%)	30.2	16.2	38.0		12.7	35.0	
TIMING OF INITIATION OF RRT							
Late (KDIGO stage≥ 3) (%)	54.1	58.9	51.6	0.087	61.1	58.8	0.735

respectively. MAKE was mainly determined by mortality (Fig. 4). MAKE was more frequent in patients with prior CKD stage <3 compared to patients with preexisting CKD stage ≥3 (Table 3).

5.4 VARIABLES ASSOCIATED WITH MAKE AT 1 YEAR

In univariate analysis, variables associated with MAKE at 1 year were the absence of preexisting CKD, severity of illness on ICU admission and at initiation of RRT (based on SAPS II and SOFA scores, mechanical ventilation, hemodynamic instability with need for vasoactive medication, anemia, low platelet count, acidosis and hyperlactatemia), oliguria, serum creatinine and continuous RRT modality at initiation of RRT (Table 1). On the basis of this univariate analysis we analyzed associations in a multivariate logistic regression model. After adjustment for confounding covariates, we found that preexisting kidney disease, initial RRT modality and timing of initiation of RRT were not associated with MAKE at 1 year (full model provided in Additional file 1: Table S2).

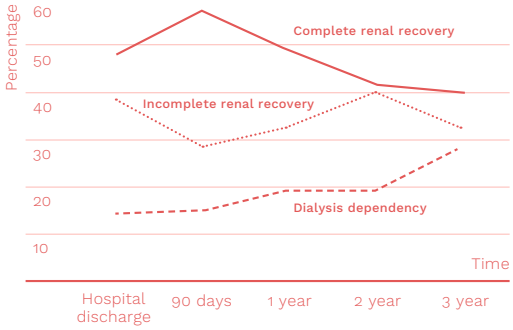
6. Discussion

We conducted a 8-year analysis in more than 23,000 first ICU admissions and found that AKI-RRT occurred in 5.5% of patients admitted to the ICU. Mortality rates were high with almost 60% of the patients dying during hospital stay and approximately an additional 10% per year of the hospital survivors in the years following discharge. Apart from advancing age and increased severity of illness, CRRT as initial RRT modality was associated with long-term mortality. As for kidney outcomes, almost one fifth of the AKI-RRT hospital survivors had ESRD at 1 year. Kidney recovery in hospital survivors after AKI-RRT was determined by preexisting renal comorbidity and diabetes mellitus. Finally, after adjustment for covariates, the occurrence of MAKE was not associated with preexisting CKD, timing of iniation of RRT, or RRT modality.

The occurrence rate and mortality of our cohort are concordant with data reported by units in other developed countries [2, 23, 24]. Similarly to others and not surprisingly, long-term mortality was was associated not only with advanced age but also varibles depicting severity of illness and accompanying haemodynamic instability: use of mechanical ventilation, vasoactive agents, and a positive fluid balance. The association of CRRT as initial modality of RRT with long-term mortality fits in this concept. In our unit, all modalities are used, and CRRT is used as initial modality in patients who are in severe shock, or for whom slow fluid removal is warranted. When patient's condition improves, the modality is switched to SLEDD or IHD. In other words, choice of the initial modality may serve as a surrogate for severity of illness. Our findings are similar to those in a recent study where RRT modality was also chosen on basis of the hemodynamic status of the patient, but they are in contrast to those in other cohort studies [8, 10, 25, 26, 27]. The recently published studies on timing of RRT by Wald et al as well as the ELAIN and Artificial Kidney Initiation in Kidney Injury (AKIKI) studies, also illustrate the complexity of the impact of timing on outcomes.

Fig. 3.

Renal recovery was defined as complete, when estimated glomerular filtration rate (eGFR) was within 25% from baseline eGFR. Incomplete kidney recovery was defined as those patients patients with an eGFR decrease of 25% or more from baseline eGFR without need for dialysis. Dialysis dependency was defined as end-stage renal disease and the permanent need for renal replacement therapy for > 3 months.



	COMPLETE RENAL RECOVERY	INCOMPLETE RENAL RECOVERY	DIALYSIS DEPENDENCY
Hospital discharge (%)	47.8	38.4	13.8
90 days (%)	56.7	28.1	15.2
1 year (%)	48.4	32.6	19.0
2 year (%)	41.5	39.5	19.0
3 year (%)	39.8	32.0	28.1

Table 2.

Renal recovery (complete and incomplete) versus dialysis dependency at 1 year in patients with reference serum creatinine values.

Statistically significant data (P<0.05) are presented in bold.

Evaluation II, **CKD** | Chronic Kidney Disease, **CRRT** | Continuous Renal Replacement Therapy, **eGFR** | estimated glomerular filtration ratio, **ICU** | intensive care unit, **IHD** | intermittent hemodialysis, **IQR** | interquartile range, **KDIGO** | Kidney Disease: Improving Global Outcomes, **RRT** | renal replacement therapy, **SAPS II** | Simplified Acute Physiology Score II, **SLEDD** | Slow Extended Daily Dialysis, **SOFA** | Sepsis-related Organ failure Assessment score, a Early (KDIGO stage <3 at initiation RRT), Late (KDIGO stage ≥3 at initiation of RRT).

	COMPLETE RENAL RECOVERY	INCOMPLETE RENAL RECOVERY	DIALYSIS DEPENDENCY	P
N (%)	89 (48.4)	60 (32.6)	35 (19.0)	
DEMOGRAPHIC DATA				
Age (year)	67 (57,75)	64 (53,75)	66 (55.75)	0.682
Gender (male, %)	64.0	80.0	57.1	**0.039**
Black (%)	0	0	0	NA
COMORBID CONDITIONS				
Diabetes mellitus (%)	32.6	21.7	57.1	**0.002**
eGFR (mL/min/1.73m²)	60.6 (43.0,77.2)	73.6 (56.0,95.4)	44.6 (27.1,67.4)	**<0.001**
CKD baseline stage≥3 (%)	49.4	28.3	69.6	**0.013**
Serum creatinine baseline (mg/dL)	1.17 (0.94,1.56)	1.05 (0.83,1.29)	1.41 (1.11,2.42)	**0.001**
CHARACTERISTICS ON ICU ADMISSION				
TYPE OF ICU				
Medical (%)	32.2	35.0	48.5	0.246
Surgical (%)	67.8	65.0	51.5	
TIMING OF SURGERY				
Urgent (%)	55.4	64.1	70.6	0.459
Elective (%)	44.6	35.9	29.4	
SEVERITY OF ILLNESS				
APACHE II	25 (19,35)	24 (21.27)	27 (19.31)	0.948
SAPS II	50 (35,69)	55 (43,69)	53 (44,71)	0.871
CHARACTERISTICS AT INITIATION OF RRT				
SEVERITY OF ILLNESS				
SOFA	8 (5,12)	9 (5,12)	5 (5,11)	0.736
SOFA non-renal	5 (2,9)	7 (2,9)	2 (1,7)	0.727
Mechanical ventilation (%)	78.2	85.0	64.5	0.082
Vasoactive medication (%)	43.7	55.0	35.5	0.172
RENAL CHARACTERISTICS				
Oliguria (%)	39.5	41.5	69.0	**0.019**
Fluid balance (ml)	1774 (997,3016)	2546 (1364,3551)	2713 (2103,4534)	0.059
Urine output (ml)	768 (253,1496)	665 (351,1225)	219 (98,1080)	0.052
Diuretics (%)	63.2	58.6	40.0	0.084
ICU to RRT length-of-stay (days)	3 (1,4)	3 (2,9)	2 (0,4)	0.606
LABORATORY PARAMETERS AT INITIATION OF RRT				
Serum Hemoglobin (g/dL)	9.8 (8.9,10.8)	9.3 (8.3,10.5)	9.6 (8.3,10.6)	0.241
Platelets (x 10^3/mm^3)	143 (80,195)	164 (87,272)	198 (90,265)	0.214
Serum Sodium (mmol/L)	136 (132,140)	140 (136,142)	139 (133,142)	**0.011**
Serum Potassium (mmol/L)	5.0 (4.4,5.5)	4.9 (4.2,5.3)	4.7 (4.2,5.1)	0.264
Serum Chloride (mmol/L)	100 (96,105)	102 (97,108)	101 (97,108)	0.081
Serum Urea (g/dL)	1.32 (1.09,1.715)	1.27 (0.92,1.78)	1.34 (1.03,1.97)	0.664
Serum Creatinine (mg/dL)	4.23 (3.27,5.05)	3.95 (3.07,5.08)	4.73 (3.37,6.54)	0.194
Serum Albumin (g/dL)	2.3 (2.0,2.8)	2.3 (1.9,2.6)	2.8 (2.2,3.3)	0.074
Lactate (mg/dL)	17 (11,33)	16 (11,83)	11 (7,94)	0.259
pH	7.34 (7.29,7.39)	7.33 (7.25,7.39)	7.33 (7.24,7.38)	0.481
Base Excess	-4.0 (-6.6,-1.6)	-4.6 (-6.5,-2.9)	-4.5 (-7.3,-3.3)	0.628
RRT MODALITY				
IHD (%)	73.0	68.3	74.3	
SLEDD (%)	14.6	16.7	8.6	**0.799**
CRRT (%)	12.4	15.0	17.1	
TIMING OF INITIATION OF RRT				
Early (%)	46.1	35.0	50.0	**0.309**
Late (%)	53.9	65.0	50.0	

While two of these studies could demonstrate no effect of timing at all, the ELAIN study showed a marked survival benefit for early initiation. Differences between these studies were the definition of early and late initiation, as well as the patient's characteristics (surgical versus general ICU), modalities used (CRRT in ELAIN versus all modalities in the other studies), and single center observation (ELAIN) versus multicenter studies (Wald and AKIKI) [28-30].

We found that, among 1-y survivors with known reference serum creatinine, only 50% had complete recovery of kidney function. With a dialysis dependency rate of 9.0% in survivors at day 90, our findings were lower to those reported in the Finnish Acute Kidney Injury (FINNAKI) study (18.9% at 90 days), and higher than in the RENAL study (5.6% at 90 days) and the IVOIRE study (1.4%) [2, 23, 31]. The FINNAKI, RENAL and IVOIRE trial used CRRT only, while we started CRRT in only one fifth of patients.

Interestingly, as dialysis dependency was predominantly associated with comorbidities such as diabetes and CKD, patients with acute-on-chronic kidney disease face a significant risk of developing ESRD. This is similar to findings in other cohort studies and meta-analyses [7, 25, 32, 33].

As many as one third of patients in our cohort had incomplete renal recovery. Follow up of patients in the RENAL study also revealed that a large proportion of AKI-RRT survivors had albuminuria and decreased eGFR [34]. Close follow-up and interventions aimed at preserving kidney function may positively impact on long-term outcomes. Similar to data reported in the USA [35], only 34.0% of AKI-RRT survivors in our cohort had follow up of kidney function by a nephrologist. In our hospital, follow-up by a nephrologist is not protocol-driven but depends on the clinical and renal status of the patient. So, how this possibly impacted kidney outcome and survival is not clear. Especially in patients with acute-on-chronic disease, more standardized kidney follow-up by a general practitioner or nephrologist may be appropriate.

After adjustment for covariates, MAKE was not associated with the classic determinants of outcome such as preexisting CKD, timing of RRT or modality of RRT. Our results demonstrate the benefits and limitations of the use of MAKE as a composite endpoint in AKI studies. MAKE is a clearly defined and a clinically important endpoint. Compared with single outcome endpoints, it captures a greater proportion of patients with poor long-term outcomes turning MAKE into a relevant endpoint. However, detailed evaluation of this outcome parameter necessitates the presentation of the individual components [15, 36-39].
In this study, MAKE was mainly determined by variables associated with its biggest individual component, mortality. Not surprisingly, variables associated with mortality in univariate analysis were also associated with MAKE: increased severity of illness scores and mechanical ventilation but also the presence of haemodynamic instability at initiation of RRT, depicted by the use of vasoactive medication, hyperlactatemia, acidosis and a positive fluid balance.

Fig. 4.

The composite endpoint major adverse kidney events (MAKE) comprised of the components death, dialysis dependency and incomplete renal recovery. Renal recovery was defined as incomplete, when estimated glomerular filtration rate (eGFR) decreased 25% or more from baseline eGFR, without need for dialysis. Dialysis dependency was defined as end-stage renal disease and permanent need for renal replacement therapy for > 3 months; CKD chronic kidney disease.

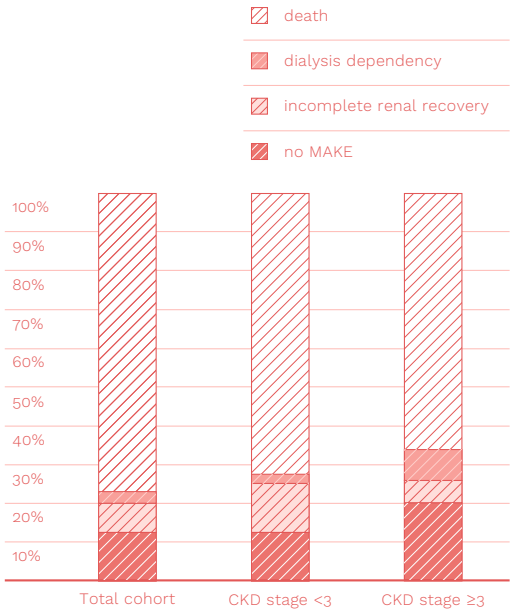


Table 3.

Renal recovery and development of end-stage renal disease in patients with acute- on-chronic kidney disease versus patients without preexisting CKD (subgroup analysis in patients with known reference baseline serum creatinine concentration).

Statistically significant data (P<0.05) are presented in bold.

CKD | chronic kidney disease, KDIGO | Kidney Disease: Improving Global Outcomes, MAKE | major adverse kidney events

Renal recovery was defined as complete when estimated glomerular filtration rate (eGFR) was within 25% from baseline eGFR. Incomplete kidney recovery was defined as patients with an eGFR decrease of 25% or more from baseline eGFR without need for dialysis. Dialysis dependency was defined as end-stage kidney disease and permanent need for RRT for > 3 months;

	TOTAL	PREEXISTING CKD STAGE <3	PREEXISTING CKD STAGE ≥3	P
KIDNEY OUTCOME				
HOSPITAL DISCHARGE				
Complete renal recovery (%)	47.8	47.2	51.3	
Incomplete renal recovery (%)	38.4	45.7	32.3	0.055
Dialysis dependency (%)	13.8	7.1	14.6	
90 DAY				
Complete renal recovery (%)	56.7	55.8	65.2	
Incomplete renal recovery (%)	28.1	34.6	15.2	**0.010**
Dialysis dependency (%)	15.2	9.6	19.7	
1 YEAR				
Complete renal recovery (%)	48.4	47.4	57.1	
Incomplete renal recovery (%)	32.6	45.3	22.1	**0.001**
Dialysis dependency (%)	19.0	7.4	20.8	
2 YEAR				
Complete renal recovery (%)	41.5	34.7	57.1	
Incomplete renal recovery (%)	39.5	61.1	22.2	**<0.001**
Dialysis dependency (%)	19.0	4.2	20.6	
3 YEAR				
Complete renal recovery (%)	39.8	39.1	51.0	
Incomplete renal recovery (%)	32.0	51.6	15.7	**<0.001**
Dialysis dependency (%)	28.1	9.4	33.3	
MAKE				
Hospital discharge (%)	83.1	87.3	51.0	**<0.001**
90 days (%)	86.0	81.9	78.2	0.280
1 year (%)	87.5	87.4	79.4	**0.010**
2 years (%)	92.4	92.4	84.2	**0.002**
3 years (%)	93.7	92.4	88.5	0.124

This study has several strengths. First, it describes an up to 8-year follow-up period in a large cohort of patients with a heavy burden of disease. Secondly, apart from the classical mortality rates, we also report detailed information concerning possible determinants of outcome in ICU patients with AKI treated with RRT such as preexisting CKD, timing of initiation of RRT and initial modality of RRT. Further, (in)complete renal recovery and dialysis dependency are extensively described. By emphasizing the risk of development of ESRD not only in patients with a single AKI-RRT episode but also in patients with acute-on-chronic kidney disease, this study provides a key role for nephrological follow-up in such a cohort of patients. Finally, this study is one of the first to report on the recently proposed composite endpoint MAKE. The composite endpoint MAKE was addressed in detail, not only revealing its benefits but also highlighting its limitations in this setting. As the study is monocentric, the conclusions cannot automatically be extended to other ICU's. Therefore, generalization of these findings must be done with caution.

This cohort study has limitations. First, owing to its observational design, we cannot exclude that there were unmeasured confounders. Second, the data reflect the practice at a single tertiary care center and may therefore lack external validity. However, the reported prevalence of 5.5% of AKI-RRT and the hospital mortality rate in this study cohort are in line with data reported by units in other developed countries [2, 27]. Third, we could include only all consecutive AKI-RRT patients present in the electronic PDMS, owing to its gradual introduction. Similarly, patients who, because of therapeutic restrictions were not started on RRT were not included in this analysis. Fourth, we only had a reference creatinine in 63.4% of patients. Therefore, renal recovery and MAKE was assessed in only a subgroup of patients. Because patients with absent documentation of a baseline serum creatinine more likely have normal kidney function, this analysis was done in a patient cohort with presumably a higher-than-normal proportion of patients with preexisting CKD. This may have impacted on our findings. To correct for possible bias, we performed a sensitivity analysis excluding baseline kidney function from the cox regression and multivariate analyses. This intervention did not change the HRs and ORs of the covariates included in the model. Therefore, we may conclude that the possibility of bias induced by this subgroup analysis may be limited.

7. Conclusions

We demonstrated a poor long-term survival after AKI-RRT associated with advancing age and clinical status at initiation of RRT. Initiation with CRRT, a surrogate for severity of illness, was associated with adverse outcome. Renal recovery was limited and associated with CKD and diabetes. Patients with acute-on-chronic disease frequently developed ESRD, making nephrological follow-up imperative. The majority of patients were classified as MAKE at 1 year. MAKE was determined mainly by its biggest component, mortality. CKD as well as timing and modality of RRT were not associated with MAKE.

ACKNOWLEDGEMENTS

We thank Chris Danneels and Veerle Brams for data retrieval from the PDMS and their help in setting up the database.

AUTHORS' CONTRIBUTIONS

WDC helped to design the study, participated in data collection and analysis, made the first draft of the paper and revised the manuscript. JV, VS and SC participated in data collection and reviewed the first draft of the paper. AD, RV, JDW and JDC helped to design the study and revised the manuscript. EH had the original idea for the study, helped to design it, participated in analysis and revised the manuscript. All authors read and approved the final manuscript.

AUTHOR'S INFORMATION

All authors attest to the originality of the text, and the originality of any and all supporting tables and images. All authors made material contributions to this manuscript according to the rules of authorship of the Critical Care Journal.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ETHICS APPROVAL

The study was approved by the Ethics Committee of the Ghent University Hospital and was conducted in accordance with the declaration of Helsinki. The need for informed consent was waived for this study.

REFERENCES

[1] Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D et al: Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015, 41(8):1411-1423.

[2] Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, Haapio M, Inkinen O, Parviainen I, Suojaranta-Ylinen R et al: Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 2013, 39(3):420-428.

[3] Kellum JA, Angus DC: Patients are dying of acute renal failure. Crit Care Med 2002, 30(9):2156-2157.

[4] Hoste EA, Schurgers M: Epidemiology of acute kidney injury: how big is the problem? Crit Care Med 2008, 36(4 Suppl):S146-151.

[5] Elseviers MM, Lins RL, Van der Niepen P, Hoste E, Malbrain ML, Damas P, Devriendt J, Investigators S: Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. Critical Care 2010, 14(6).

[6] Chawla LS, Eggers PW, Star RA, Kimmel PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014, 371(1):58-66.

[7] Rimes-Stigare C, Frumento P, Bottai M, Martensson J, Martling CR, Bell M: Long-term mortality and risk factors for development of end-stage renal disease in critically ill patients with and without chronic kidney disease. Crit Care 2015, 19:383.

[8] Bell M, Swing, Granath F, Schon S, Ekbom A, Martling CR: Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med 2007, 33(5):773-780.

[9] Uchino S, Bellomo R, Kellum JA, Morimatsu H, Morgera S, Schetz MR, Tan I, Bouman C, Macedo E, Gibney N et al: Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. Int J Artif Organs 2007, 30(4):281-292.

[10] Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, Cass A, Gallagher M: Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med 2013, 39(6):987-997.

[11] Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P et al: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet 2006, 368(9533):379-385.

[12] Wald R, Bagshaw SM: The Timing of Renal Replacement Therapy Initiation in Acute Kidney Injury. Seminars in nephrology 2016, 36(1):78-84.

[13] Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE: Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int 2009, 76(10):1089-1097.

[14] Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, Collins AJ: Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 2009, 20(1):223-228.

[15] Billings FTt, Shaw AD: Clinical trial endpoints in acute kidney injury. Nephron Clin Pract 2014, 127(1-4):89-93.

[16] De Corte W, Vuylsteke S, De Waele JJ, Dhondt AW, Decruyenaere J, Vanholder R, Hoste EA: Severe lactic acidosis in critically ill patients with acute kidney injury treated with renal replacement therapy. J Crit Care 2014, 29(4):650-655.

[17] Reynvoet E, Vandijck DM, Blot SI, Dhondt AW, De Waele JJ, Claus S, Buyle FM, Vanholder RC, Hoste EA: Epidemiology of infection in critically ill patients with acute renal failure. Crit Care Med 2009, 37(7):2203-2209.

[18] Zavada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, Bellomo R, Kellum JA, investigators AKI: A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol Dial Transplant 2010, 25(12):3911-3918.

[19] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements 2013, 3(1):1-150.

[20] Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. Crit Care Med 1985, 13(10):818-829.

[21] Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993, 270(24):2957-2963.

[22] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996, 22(7):707-710.

[23] Investigators RRTS, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J et al: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009, 361(17):1627-1638.

[24] Network VNARFT, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E et al: Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008, 359(1):7-20.

25] Venot M, Weis L, Clec'h C, Darmon M, Allaouchiche B, Goldgran-Toledano D, et al. Acute kidney injury in severe sepsis and septic shock in patients with and without diabetes mellitus: a multicenter study. PLoS One. 2015;10(5)e0127411

[26] Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R: Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med 2008, 36(2):610-617.

[27] Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E et al: Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005, 294(7):813-818.

[28] Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A, Thorpe K, McIntyre L, Lamontagne F, Soth M et al: Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney Int 2015, 88(4):897-904.

[29] Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, Boanta A, Gerss J, Meersch M: Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA 2016, 315(20):2190-2199.

[30] Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D et al: Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med 2016.

[31] Joannes-Boyau O, Honore PM, Perez P, Bagshaw SM, Grand H, Canivet JL, Dewitte A, Flamens C, Pujol W, Grandoulier AS et al: High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med 2013, 39(9):1535-1546.

[32] Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordonez JD, Go AS: Nonrecovery of kidney function and death after acute on chronic renal failure. Clin J Am Soc Nephrol 2009, 4(5):891-898.

[33] Sawhney S, Mitchell M, Marks A, Fluck N, Black C: Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. BMJ Open 2015, 5(1):e006497.

[34] Gallagher M, Cass A, Bellomo R, Finfer S, Gattas D, Lee J, Lo S, McGuinness S, Myburgh J, Parke R et al: Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLoS medicine 2014, 11(2):e1001601.

[35] Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE: The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011, 79(12):1361-1369.

[36] Kellum JA: How can we define recovery after acute kidney injury? Considerations from epidemiology and clinical trial design. Nephron Clin Pract 2014, 127(1-4):81-88.

[37] Palevsky PM, Molitoris BA, Okusa MD, Levin A, Waikar SS, Wald R, Chertow GM, Murray PT, Parikh CR, Shaw AD et al: Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. Clin J Am Soc Nephrol 2012, 7(5):844-850.

[38] Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS et al: Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013, 17(1):R25.

[39] Cordoba G, Schwartz L, Woloshin S, Bae H, Gotzsche PC: Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. Bmj 2010, 341:c3920.

Table S1.

Cox proportional hazard model.

GFR | Glomerular Filtration Rate, **MICU** | Medical ICU, **RRT** | Renal Replacement Therapy, **CRRT** | Continuous Renal Replacement Therapy

* at initiation of RRT
** KDIGO stage ≥3

	MORTALITY		
VARIABLES	HAZARD RATIO	95% CONFIDENCE INTERVAL	*P*
AGE	1.021	1.011, 1.030	***<0.001***
GENDER	1.016	0.819, 1.261	*0.885*
GFR BASELINE	0.998	0.992, 1.005	*0.573*
ADMISSION TO MICU	1.520	1.232, 1.875	***<0.001***
VENTILATION*	0.928	0.646, 1.334	*0.687*
VASOPRESSOR USE*	1.351	1.065, 1.713	***0.013***
SERUM CREATININE*	0.789	0.712, 0.875	***<0.001***
SERUM UREA*	0.993	0.962, 1.024	*0.650*
SERUM HEMOGLOBIN	1.002	1.000,1.004	*0.112*
BLOOD PLATELETS*	0.998	0.997,0.999	***<0.001***
SERUM SODIUM*	1.036	1.016,1.057	***<0.001***
SERUM POTASSIUM*	1.003	0.999,1.008	*0.158*
SERUM CHLORIDE*	0.992	0.981,1.002	*0.129*
BASE EXCESS*	0.977	0.957,0.997	***0.022***
CRRT AS INITIAL RRT MODALITY	1.570	1.202,2.050	***0.001***
LATE INITIATION OF RRT**	1.279	0.943,1.734	*0.114*

Table S2.

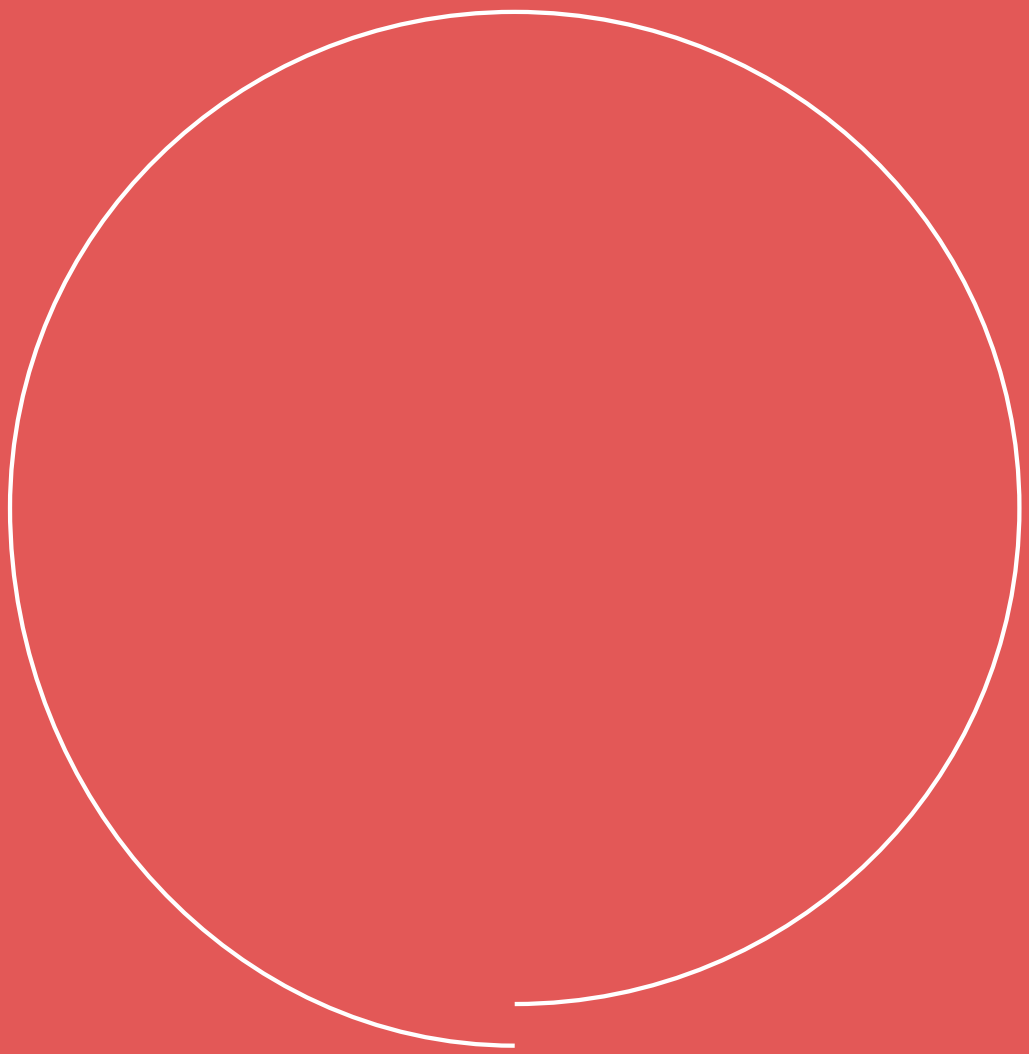
Multivariate regression analysis: MAKE at 1 year.

GFR | Glomerular Filtration Rate, MICU | Medical ICU, RRT | Renal Replacement Therapy, CRRT | Continuous Renal Replacement Therapy

Model MAKE 1 year: Goodness of fit (Hosmer and Lemeshow) Chi2 = 4.347, df=8, P= 0.825. Overall percentage correctly predicted = 83.3%.

* at initiation of RRT
** KDIGO stage ≥3

	MAKE 1 YEAR		
VARIABLES	ODDS RATIO	95% CONFIDENCE INTERVAL	*P*
AGE	1.029	1.003,1.056	*0.027*
GENDER	1.205	0.679,2.136	*0.524*
GFR BASELINE	1.005	0.987, 1.024	*0.568*
ADMISSION TO MICU	1.987	1.056,3.737	***0.033***
VENTILATION*	0.526	0.253,1.096	*0.860*
VASOPRESSOR USE*	1.087	0.599,1.974	*0.783*
OLIGURIA*	0.958	0.537,1.708	*0.884*
DIURETICS*	1.274	0.713,2.277	*0.414*
SERUM CREATININE*	0.923	0.751, 1.133	*0.444*
SERUM UREA*	0.919	0.641,1.318	*0.647*
SERUM HEMOGLOBIN	1.045	0.881,1.240	*0.612*
BLOOD PLATELETS*	1.000	0.997,1.002	*0.687*
SERUM SODIUM*	1.020	0.967,1.077	*0.464*
SERUM POTASSIUM*	0.962	0.698,1.325	*0.812*
SERUM CHLORIDE*	1.003	0.974,1.033	*0.825*
PH*	1.000	0.994,1.006	*0.965*
LACTATE*	1.000	1.000,1.000	*0.198*
BASE EXCESS*	1.016	0.958,1.078	*0.593*
CRRT AS INITIAL RRT MODALITY*	0.829	0.303,2.264	*0.714*
LATE INITIATION OF RRT**	0.763	0.348,1.674	*0.500*



6

Long-term quality of life in critically ill patients with acute kidney injury treated with renal replacement therapy: a matched cohort study.

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PUBLISHED IN
Crit Care. 2015 Aug 6;19:289.

INTRODUCTION

AKI is a common complication in ICU patients and associated with increased morbidity and mortality. We compared long-term outcome and quality of life (QOL) in ICU patients with AKI treated with RRT with matched non AKI-RRT patients.

METHODS

During 1 year adult ICU patients consecutively were included in a prospective cohort study. AKI-RRT patients alive at 1 year and 4 years were matched with non AKI-RRT survivors from the same cohort in a 1:2 (1 year) and 1:1 (4 years) ratio on gender, age, APACHE II score, and admission category. QOL was assessed by the EuroQoL-5D and the Short Form-36 survey before ICU admission and at 3 months, 1 and 4 years after ICU discharge.

RESULTS

Of 1953 patients, 121 (6.2%) had AKI-RRT. AKI-RRT hospital survivors (44.6%; N=54) had a 1-year and 4-year survival rate of 87.0% (N=47) and 64.8% (N=35) respectively. Forty-seven 1-year AKI-RRT patients were matched with 94 1-year non AKI-RRT patients. Of 35 4-years survivors 3 refused further cooperation, 3 were lost-to-follow-up, and 1 had no control. Finally, 28 4-years AKI-RRT patients were matched with 28 non AKI-RRT patients. During ICU stay, 1-year and 4-years AKI-RRT patients had more organ dysfunction compared to their respective matches (SOFA scores 7 vs. 5, $P<0.001$; 7 vs. 4, $P<0.001$). Long-term QOL was, however, comparable between both groups but lower than in the general population. QOL decreased at 3 months, improved after 1 and 4 years but remained under baseline level. Respectively 1 and 4 years after ICU discharge, 19.1% and 28.6% of AKI-RRT survivors remained RRT dependent, and 81.8% and 71% of them were willing to undergo ICU admission again if needed.

CONCLUSION

In long-term critically ill AKI-RRT survivors, QOL was comparable to matched long-term critically ill non AKI-RRT survivors, but lower than in the general population. The majority of AKI-RRT patients wanted to be readmitted to the ICU when needed, despite a higher severity of illness compared to matched non AKI-RRT patients, and despite the fact that one quarter had persistent dialysis dependency.

KEY MESSAGE

Long-term critically ill AKI-RRT survivors have comparable quality of life to matched long-term critically ill survivors without RRT. In case of deterioration, majority of the patients prefer to be readmitted to the ICU department.

1. Introduction

Acute kidney injury treated with renal replacement therapy (AKI-RRT) affects approximately 5-10% of ICU patients [1]. These patients are amongst the most severely ill patients in the ICU, as may be illustrated by the 50% in-hospital mortality [2,4]. AKI-RRT patients who survive may develop chronic kidney disease, including end stage renal disease, and experience decreased long-term survival [4-8]. Therefore, to fully appreciate outcomes of critically ill AKI-RRT survivors, indices regarding long-term morbidity and QOL should also be taken into account [9,10].

Major reductions in long-term QOL in critically ill patients are seen in severe acute respiratory distress syndrome, prolonged mechanical ventilation, severe sepsis, and after major trauma, all conditions frequently associated with AKI-RRT [11]. Data regarding QOL in AKI-RRT patients show that these patients have a decreased QOL compared to the general population but perceive QOL as good [12, 13]. However, these studies were either retrospective [14-17], evaluated QOL after a short term [12-15, 17-21], lacked baseline QOL assessment [12-15, 18,22], or dated back more than a decade [14-16, 18,23]. It is also unclear whether impairment in long-term QOL is the consequences of critical illness, AKI-RRT, pre-existing co-morbidities, or a combination of these.

The aim of the present study was to assess long-term outcomes and QOL of critically ill AKI-RRT patients at baseline, and at 3 months, 1 year and 4 years after ICU discharge and to compare QOL with a cohort of matched non AKI-RRT patients [24].

2. Methods

2.1 DESIGN, PATIENTS, AND SETTING

The cohort described in this study is a subgroup of a prospective observational cohort. During one year (March 2008 to March 2009), all consecutively admitted adult patients at the 14-bed medical (MICU), the 22-bed surgical ICU (SICU), and the 6-bed burn unit of the Ghent University Hospital, Belgium, were screened to study QOL and cost-effectiveness of intensive care [25]. Exclusion criteria were age < 16 y and admission to the ICU after cardiac surgery. In case of multiple ICU admissions, only the first was considered.

In this study, only AKI-RRT patients of the larger cohort were included. Chronic hemodialysis patients were excluded. The attending critical care physician and consulting nephrologist assessed indication for RRT and modality.

To study the impact of RRT on long-term outcome and QOL, we performed a matched cohort study, according to the STROBE guidelines [26]. Included AKI-RRT patients alive at 1 year after hospital discharge were defined as exposed patients and individually matched with 1-year non AKI-RRT survivors (defined as non-exposed patients) from the same cohort. Being a patient in the non AKI-RRT group did not imply normal kidney function: it implied no treatment with RRT. To correct for possible bias, we excluded patients who needed RRT but who did not receive RRT due to therapeutic restrictions. Equally, AKI-RRT patients alive at time of this study (average 4 years later) were individually matched with 4-years non AKI-RRT survivors. The exposed to nonexposed ratio was aimed at 1:2 to reduce risk of selection bias. When there were more than 2 nonexposed patients for an exposed patient, only the nonexposed patient with the best overall match was selected. If an exposed patient could only be properly matched to 1 nonexposed patient, we accepted matching in a 1:1 ratio for the respective cohort in order to avoid an imbalance of characteristics and to retain the best possible matching. Matching was based on gender, age (±5 years), APACHE II score (± 5), and admission category.

2.2 DATA COLLECTION AND DEFINITIONS

Variables collected within the first 24 hours of ICU admission included age, gender, body mass index, personal, proxy, and family practitioner contact data, living situation, activity of daily living, co-morbidity as measured by the Charlson co-morbidity index [27], hospitalization in the last 6 months, main reason for ICU admission, APACHE II score [28], SOFA score [29], need for mechanical ventilation, use of any vasopressors, and need for RRT. During ICU stay SOFA scores, need for mechanical ventilation, vasopressors, RRT, and do-not-resuscitate codes were collected on a daily base. ICU length of stay (LOS), hospital LOS, vital status at ICU and hospital discharge, and at 3 months, 1 year and 4 years following ICU discharge were collected for each patient.

Values of serum creatinine of AKI-RRT patients were extracted from the STARRT database, which includes all relevant renal and RRT data of ICU patients with AKI–RRT treated in our hospital, and from laboratory data in control patients. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [30]. Renal recovery was defined as independence from RRT.

The study was approved by the local ethical committee (B67020072805), and conducted in accordance with the declaration of Helsinki. A signed informed consent was obtained from every included patient.

2.3 QUALITY OF LIFE

QOL was assessed by means of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36v2®) and the EuroQoL-5D (EQ-5D). The SF-36 questionnaire contains 36 items measuring 8 health domains: physical- (PF), and social functioning (SF), role limitations due to physical- (RP), or emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP), and general perception of health (GH) [31]. Two component scores,

a physical (PCS) and a mental (MCS), are calculated summary scores where respectively the physical domains (PF, RP, BP, GH) or the mental domains (VT, SF, RE, MH) will account more in the score. We assessed SF-36 as norm-based scores to be able to compare them directly with the general healthy population, with a group-level range of 47-53 considered as average or normal [31]. Group scores less than 47 indicate impaired functioning within that health domain; group scores greater than or equal to 53 should be considered average or above the normative sample.

The 36th item, health transition, provides information about perceived changes in health status. The validity and reliability of the SF-36 has been confirmed in critically ill patients, and its use is validated in face-to-face interviews, interview by phone or by sending the questionnaire by regular mail [32].

The EQ-5D is a generic QOL questionnaire that measures health in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [33]. Each dimension has three levels: no problems, moderate problems or severe problems. On a visual analogue scale (VAS), patients can rate their perceived overall health between 0 and 100. The EQ-5D is suitable for measuring QOL in critical care [34, 35].

QOL was assessed at different time points: baseline QOL and at strictly 3 months and 1 year after ICU discharge. QOL was also assessed in August 2013, a median of 4.1 years (3.9 years – 4.3 years) after ICU discharge. Following ICU admission and study inclusion, a face-to-face interview to assess baseline QOL (defined as QOL 2 weeks before ICU admission) was done as soon as possible. This interview was preferably taken from the patient, or when impossible, from the proxy. Three months, 1 year, and 4 years after ICU discharge, patients were sent the EQ-5D and SF-36 surveys by regular mail; at 1 and 4 years, questions concerning living situation, memories, sleep quality, and willingness to be readmitted to an ICU department, were added. If the questionnaires were not returned within one month, patients or relatives were contacted by phone to assess QOL after 1 year and after 4 years. Eventually, the family practitioner was contacted.

2.4 STATISTICAL ANALYSIS

Data are expressed as median (interquartile range) (IQR) for continuous variables and as number (%) for categorical variables. QOL at the different time points and characteristics between both groups (AKI-RRT versus non AKI-RRT patients) were compared by the Mann-Whitney U test for continuous variables and by the Chi-square test for categorical variables. For long-term analysis of QOL, differences between QOL at baseline (only hospital survivors), at 3 months, at 1 and 4 years after ICU discharge were assessed by Chi-square (EQ-5D) or Friedman test (SF-36). P-values were two-sided and statistical significance was set at 0.05. All statistical analyses were done using IBM SPSS Statistics software version 21 (IBM, Armonk, New york, USA)..

3. Results

3.1 CHARACTERISTICS OF THE STUDY POPULATION

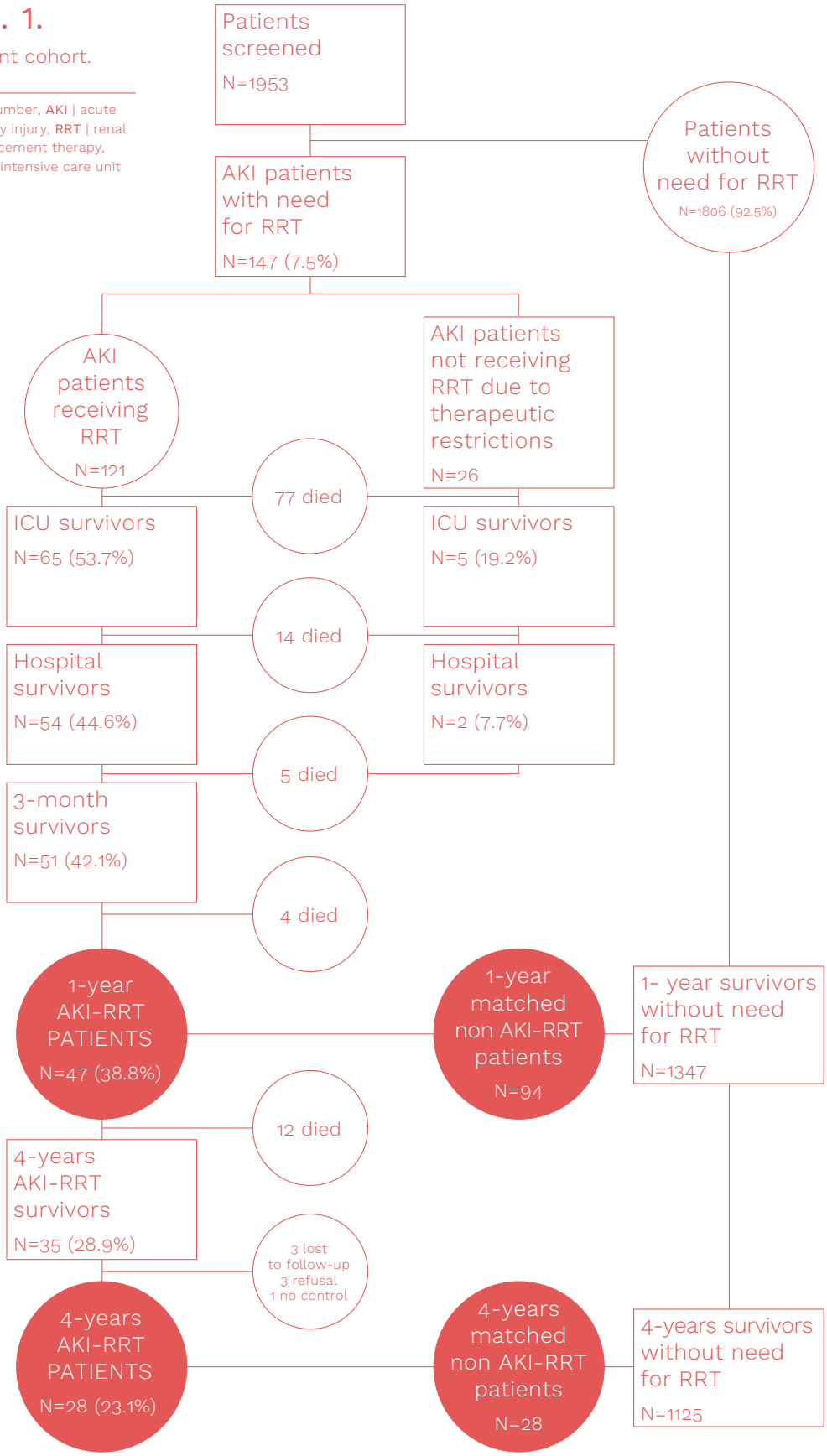
During the 1-year study period 1953 patients were included (Fig. 1.). One hundred forty-seven patients (7.5%) developed AKI with need for RRT. Of these, 121 patients (6.2%) received RRT. ICU (46.3%), hospital (55.4%), 3 months (57.9%), 1-year (61.1%) and 4-years (71.1%) mortality rates in these patients were high. Twenty-six AKI patients (1.3%) did not receive RRT due to therapeutic restrictions and were excluded for further analysis.

AKI-RRT hospital survivors (44.6%) had a 1-year and 4-years survival rate of 87.0% and 64.8% respectively. Forty-seven 1-year AKI-RRT survivors were individually matched with 94 1-year non AKI-RRT survivors (two matches for all AKI-RRT patients). Of 35 4-years survivors 3 refused further cooperation, 3 were lost-to-follow-up, and 1 had a double match. In 13 of the 28 included 4-years AKI-RRT survivors only one good match could be withhold, so matching occurred in a 1:1 ratio. Finally, 28 4-years AKI-RRT survivors were individually matched with 28 non AKI-RRT patients. AKI-RRT and

Fig. 1.

Patient cohort.

N | number, AKI | acute kidney injury, RRT | renal replacement therapy, ICU | intensive care unit



non AKI-RRT patients had similar gender, age, APACHE II score, and admission category at 1 year and 4 years **(Table 1)**.

During ICU stay, 1-year and 4-years AKI-RRT patients had higher SOFA scores compared to their respective matches, and more needed mechanical ventilation or vasopressors for a longer time **(Table 1)**.

3.2 RENAL CHARACTERISTICS AND RENAL OUTCOMES

One year AKI-RRT patients had higher baseline serum creatinine concentrations and lower eGFR compared to their matches. These measurements did not significantly differ between 4-years AKI-RRT and non AKI-RRT patients **(Table 1)**.

Respectively 12 1-year (25.5%) and 10 4-years AKI-RRT patients (35.7%) were RRT dependent at hospital discharge. Nine (19.1%) of the 1-year and 8 (28.6%) of the 4-years AKI-RRT patients remained RRT dependent over time.

3.3 QUALITY OF LIFE

An overview of the persons who rated QOL, how QOL was assessed and the number of completed QOL surveys is given in **Table 2**. Most patients rated their own QOL at the different time points, except at baseline in 1-year AKI-RRT patients.

Significant differences in QOL between AKI-RRT and non AKI-RRT survivors at each different time point were small. **Figure 2 and Figure 3** show that the 1-year AKI-RRT versus (vs) 1-year non AKI-RRT patients had comparable baseline QOL. The 1-year AKI-RRT patients were poorer emotionally at 3-months (RE 28.7 vs 38.4; P=0.035), but had a better mental score (MCS 53.3 vs 47.8; P=0.039) and less bodily pain (BP 46.5 vs 41.6; P=0.041) at 1 year **(Fig. 3)**. **Figure 4 and 5** show that the 4-years AKI-RRT vs 4-years non AKI-RRT patients were emotionally better at baseline (RE 55.9 vs 40.3; P=0.030) **(Fig. 5.)**, but had more problems with usual activities (81.0% vs 47.8%; P=0.023), pain (71.4% vs 26.1%; P=0.003) and anxiety (61.9% vs 17.4%; P=0.002) at 3 months **(Fig. 4.)**. QOL after 1 and 4 years showed no differences **(Fig. 4. and Fig. 5.)**.

Comparing QOL within each group between the different time points revealed that QOL particularly decreased after 3 months.

3.4 EVOLUTION IN QOL OVER TIME: 1 YEAR-COHORT

All 1-year AKI-RRT patients reported more problems on the EQ-5D after 3 months compared to baseline. After 1 year, they experienced fewer problems but still more than before ICU admission. The EQ-5D showed the same evolution for 1-year non AKI-RRT patients **(Supplemental File (AF)-Fig. 1A/1B)**.

The SF-36 showed significant evolutions in QOL over time for 1-year AKI-RRT patients in nearly all dimensions. QOL decreased after 3 months, improved after 1 year but without return to the baseline level. QOL also remained under the level of the average population. The same pattern, although less pronounced, was seen in 1-year non AKI-RRT patients **(Supplemental File-Fig. 2A/2B)**.

For 1-year AKI-RRT patients median VAS scores ranged from 70 (baseline), to 60 (3 months) and 70 (1 year) (P=0.048). In non AKI-RRT patients the VAS remained the same, respectively 68, 65 and 65 at baseline, 3 months and 1 year after ICU discharge (P=0.917).

3.5 EVOLUTION IN QOL OVER TIME: 4 YEARS-COHORT

Changes in QOL over time assessed by the EQ-5D were significant in AKI-RRT patients for mobility (P=0.040), usual activities (P<0.001), and anxiety (P=0.040) **(Supplemental File-Fig. 1C)** and in 4-years non AKI-RRT patients for mobility (P=0.017), and usual activities (P=0.014) with most problems at 3 months after ICU discharge followed by an improvement in QOL after 1 year **(Supplemental File-Fig. 1D)**. QOL never returned to baseline level.

The SF-36 showed that in both groups, QOL decreased after 3 months compared to baseline **(Supplemental File-Fig. 2C/2D)**. For the 4-years AKI-RRT patients, QOL improved after 1 year, especially in the mental domains. At 4 years, QOL significantly decreased mainly physically but improved or remained the same in

Table 1.

Patient characteristics at ICU admission, organ failure during ICU admission, and outcomes.

AKI | acute kidney injury, RRT | renal replacement therapy, yrs | years, IQR | interquartile range (25%-75%), N | number, BMI | body mass index, eGFR | estimated glomerular filtration rate, ICU | intensive care unit, ADL | activity of daily living, NA | not applicable, ICU | intensive care unit, APACHE | Acute Physiology and Chronic Health Evaluation, SOFA | Sequential Organ Failure Assessment, LOS | length of stay, DNR | do-not-resuscitate, NA | not applicable

* Serum creatinine at baseline was defined as serum creatinine 6 months before ICU admission. Values were missing in 27 of the 1-year AKI-RRT patients, in 14 of the 94 1-year non AKI-RRT patients, in 21 of the 4-years AKI-RRT patients, and in 4 the 4-years non AKI-RRT patients

	1-YEAR AKI-RRT PAT. (N=47)	1-YEAR NON AKI-RRT PAT. (N=94)	*P*	4-YEAR AKI-RRT PAT. (N=28)	4-YEAR NON AKI-RRT PAT. (N=28)	*P*
AGE, YRS (median, IQR)	57 (45-69)	57 (48-70)	*0.897*	54 (45-66)	53 (45-68)	*0.718*
MALE GENDER, *N (%)*	31 (66.0)	62 (66.0)	*0.999*	16 (57.1)	16 (57.1)	*0.999*
BMI, KG/M² (median, IQR)	26.2 (22.8-29.7)	25.9 (22.0-29.4)	*0.444*	27.3 (22.9-31.6)	24.5 (22.9-27.8)	*0.092*
SERUM CREATININE BASELINE (mg/dL, median, IQR)*	1.14 (0.94-1.51)	0.82 (0.66-1.04)	*0.001*	0.97 (0.80-1.26)	0.78 (0.65-1.11)	*0.062*
EGFR BASELINE (mL/min per 1.73 m², median, IQR)*	86 (71-100)	100 (83-116)	*0.007*	99 (85-109)	102 (87-116)	*0.629*
LIVES AT HOME BEFORE ADMISSION, *N (%)*	45 (95.7)	90 (95.75)	*0.999*	26 (92.9)	27 (96.4)	*0.553*
ADL, *N (%)*	——	——	——	——	——	——
No limitations	25 (53.2)	47 (50.0)	*0.721*	18 (63.4)	21 (75.0)	*0.383*
Moderate limitations	19 (40.4)	42 (44.7)	*0.631*	7 (25.0)	7 (25.0)	*0.999*
Chair-bound	0 (0)	3 (3.2)	*0.216*	0 (0)	0 (0)	*NA*
Bedridden	3 (6.4)	2 (2.1)	*0.198*	3 (10.7)	0 (0)	*<0.001*
HOSPITALIZATION IN LAST 6 MONTHS BEFORE ICU, *N (%)*	20 (42.6)	46 (48.9)	*0.474*	10 (35.7)	14 (50.0)	*0.280*
CHARLSON COMORBIDITY INDEX (median, IQR)	1 (0-3)	2 (0-3)	*0.115*	0 (0-2)	2 (0-3)	*0.110*
TYPE OF ADMISSION, N (%)						
MEDICAL	32 (68.1)	67 (71.3)	*0.696*	18 (64.3)	18 (64.3)	*0.999*
SCHEDULED SURGERY	1 (2.1)	4 (4.3)	*0.519*	0 (0)	4 (14.3)	*0.038*
EMERGENCY SURGERY	10 (21.3)	18 (19.1)	*0.765*	7 (25.0)	3 (10.7)	*0.163*
TRAUMA	3 (6.4)	4 (4.3)	*0.376*	2 (7.1)	2 (7.1)	*0.999*
BURNS	1 (2.1)	1 (1.1)	*0.614*	1 (3.6)	1 (3.6)	*0.999*
SEVERITY OF ILLNESS AT ICU ADMISSION (FIRST 24 HOURS)						
APACHE II SCORE (median, IQR)	26 (21-31)	24 (20-30)	*0.251*	23 (20-28)	22 (18-25)	*0.362*
SOFA SCORE (median, IQR)	9 (5-11)	7 (5-10)	*0.047*	7 (4-12)	6 (4-9)	*0.139*
MECHANICAL VENTILATION, *N (%)*	29 (61.7)	49 (52.1)	*0.281*	21 (75.0)	13 (46.4)	*0.029*
VASOPRESSORS, *N (%)*	21 (44.7)	37 (39.4)	*0.545*	11 (39.3)	9 (32.1)	*0.577*
RRT, *N (%)*	11 (23.4)	0 (0)	*<0.001*	6 (21.4)	0 (0)	*0.010*
ORGAN FAILURE DURING ICU STAY						
MECHANICAL VENTILATION, *N (%)*	39 (83.0)	50 (53.2)	*<0.001*	24 (85.7)	13 (46.4)	*0.002*
LENGTH OF MECHANICAL VENTILATION, DAYS (median, IQR)	16 (3-27)	1 (0-3)	*<0.001*	18 (4-31)	0 (0-7)	*<0.001*
VASOPRESSORS, *N (%)*	36 (76.6)	42 (44.7)	*<0.001*	21 (75.0)	10 (35.7)	*0.003*
LENGTH OF VASOPRESSOR THERAPY, DAYS (median, IQR)	5 (1-8)	0 (0-3)	*<0.001*	3 (0-10)	0 (0-3)	*0.002*
RRT, *N (%)*	47 (100)	0 (0)	*<0.001*	28 (100.0)	0 (0)	*<0.001*
MEAN SOFA SCORE (median, IQR)	7 (6-9)	5 (4-7)	*<0.001*	7 (5-10)	4 (4-7)	*<0.001*

	1-YEAR AKI-RRT PAT. (N=47)	1-YEAR NON AKI-RRT PAT. (N=94)	*P*	4-YEAR AKI-RRT PAT. (N=28)	4-YEAR NON AKI-RRT PAT. (N=28)	*P*
OUTCOMES						
ICU LOS, DAYS (median, IQR)	22 (11-42)	5 (3-9)	*<0.001*	24 (13-49)	7 (3-10)	*<0.001*
READMISSIONS, *N (%)*	8 (17.0)	12 (12.8)	*0.495*	3 (10.7)	4 (14.3)	*0.686*
HOSPITAL LOS, DAYS (median, IQR)	70 (30-100)	21 (13-44)	*<0.001*	62 (20-130)	19 (10-46)	*0.003*
DNR DECISIONS, *N (%)*	4 (8.5)	3 (3.2)	*0.170*	2 (7.1)	1 (3.6)	*0.312*
LONG-TERM MORTALITY, *N (%)*	12 (25.5)	20 (21.3)	*0.570*	NA	NA	*NA*
NEED FOR RRT AT HOSPITAL DISCHARGE, *N (%)*	12 (25.5)	NA	*NA*	10 (35.7)	NA	*NA*
NEED FOR RRT AT 3 MONTHS, *N (%)*	9 (19.1)	NA	*NA*	8 (28.6)	NA	*NA*
NEED FOR RRT AT 1 YEAR, *N (%)*	9 (19.1)	NA	*NA*	8 (28.6)	NA	*NA*
NEED FOR RRT AT 4 YEARS, *N (%)*	NA	NA	*NA*	8 (28.6)	NA	*NA*
LIVING SITUATION AFTER 1 YEAR, *N (%)*	46 answers	93 answers		27 answers	26 answers	
Independent without additional help	25 (54.3)	47 (50.5)	*0.672*	16 (59.3)	14 (53.8)	*0.691*
Independent with some help	12 (26.1)	22 (23.7)	*0.754*	6 (22.2)	6 (23.1)	*0.941*
Together with relatives (others than spouse)	6 (13.0)	14 (15.1)	*0.751*	3 (11.1)	4 (15.4)	*0.646*
Special care facility	3 (6.5)	5 (5.4)	*0.786*	2 (7.4)	1 (3.8)	*0.575*
Other	0 (0)	5 (5.4)	*0.109*	0 (0)	1 (3.8)	*0.304*
LIVING SITUATION AFTER 4 YEARS, *N (%)*	NA	NA	*NA*	27 answers	26 answers	
Independent without additional help	NA	NA	*NA*	18 (66.7)	14 (53.8)	*0.340*
Independent with some help	NA	NA	*NA*	5 (18.5)	6 (23.1)	*0.682*
Together with relatives (others than spouse)	NA	NA	*NA*	2 (7.4)	5 (19.2)	*0.204*
Special care facility	NA	NA	*NA*	2 (7.4)	1 (3.8)	*0.575*
Other	NA	NA	*NA*	0 (0)	0 (0)	*0.999*

Fig. 2.

EQ-5D assessments in the 1-year cohort: Percentages of patients with some or severe problems per dimension at the 3 different time points.

☐ 47 1-year AKI-RRT patients

▨ 94 1-year non AKI-RRT patients

The X-axis represents the different dimensions of the EQ-5D. The Y-axis represents the percentages (%) of patients with some or severe problems in a respective dimension.

Only significant P-values (Chi-Square test) are shown above the respective dimensions.

QOL | quality of life, **AKI** | acute kidney injury, **RRT** | renal replacement therapy

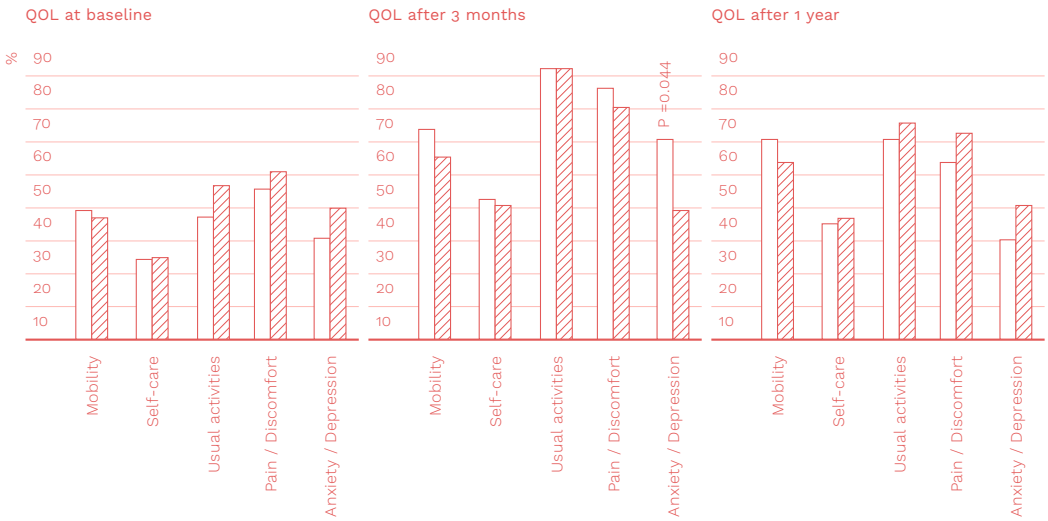


Fig. 3.

SF-36 assessments in the 1-year cohort: Norm-based median scores per domain at the 3 different time points.

☐ 47 1-year AKI-RRT patients

▨ 94 1-year non AKI-RRT patients

The X-axis represents the different domains of the SF-36. The Y-axis represents the norm-based median scores in a respective domain of the SF-36. A norm-based median score between 47-53 in a group of patients is considered as normal or average. Norm-based median scores below 47 indicate impaired functioning or below average; norm-based median scores above 53 indicate better functioning or above average.

Only significant P-values (Mann-Whitney U analysis) are shown above the respective domains.

QOL | quality of life, **AKI** | acute kidney injury, **RRT** | renal replacement therapy, **PCS** | physical component score, **MCS** | mental component score, **PF** | physical functioning, **RP** | role physical, **BP** | bodily pain, **GH** | general health, **VT** | vitality, **SF** | social functioning, **RE** | role emotional, **MH** | mental health

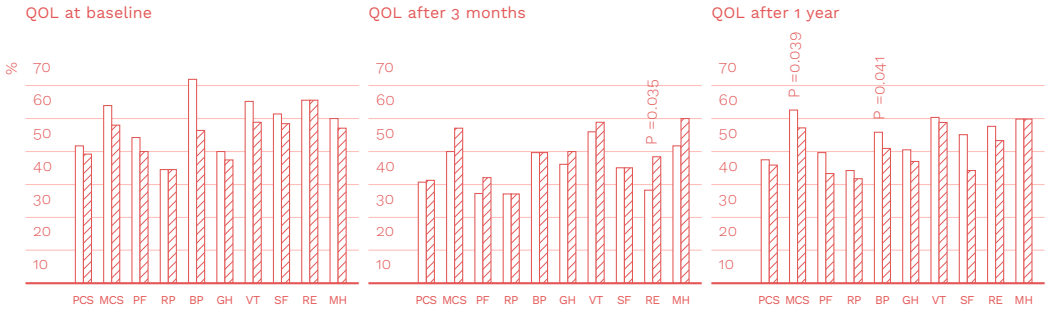


Fig. 4.

EQ-5D assessments in the 4-years cohort: Percentages of patients with some or severe problems per dimension at the 4 different time points.

The X-axis represents the different dimensions of the EQ-5D. The Y-axis represents the percentages (%) of patients with some or severe problems in a respective dimension.

Only significant P-values (Chi Square test) are shown above the respective dimensions.

QOL | quality of life, AKI | acute kidney injury, RRT | renal replacement therapy

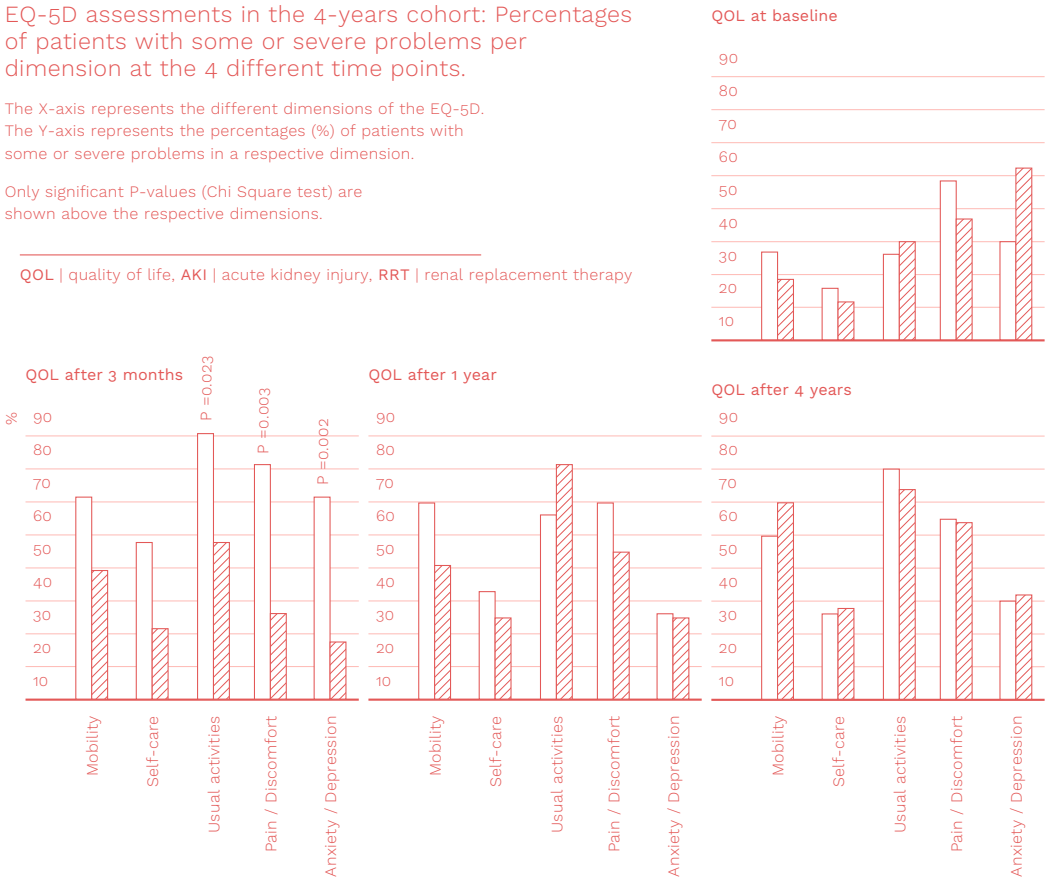


Fig. 5.

SF-36 assessments in the 4-years cohort: Norm-based median scores per domain at the 4 different time points.

The Y-axis represents the norm-based median scores in a respective domain of the SF-36. A norm-based median score between 47-53 in a group of patients is considered as normal or average. Norm-based median scores below 47 indicate impaired functioning or below average; norm-based median scores above 53 indicate better functioning or above average.

Only significant P-values (Mann-Whitney U analysis) are shown above the respective domains.

QOL | quality of life, AKI | acute kidney injury, RRT | renal replacement therapy, PCS | physical component score, MCS | mental component score, PF | physical functioning, RP | role physical, BP | bodily pain, GH | general health, VT | vitality, SF | social functioning, RE | role emotional, MH | mental health

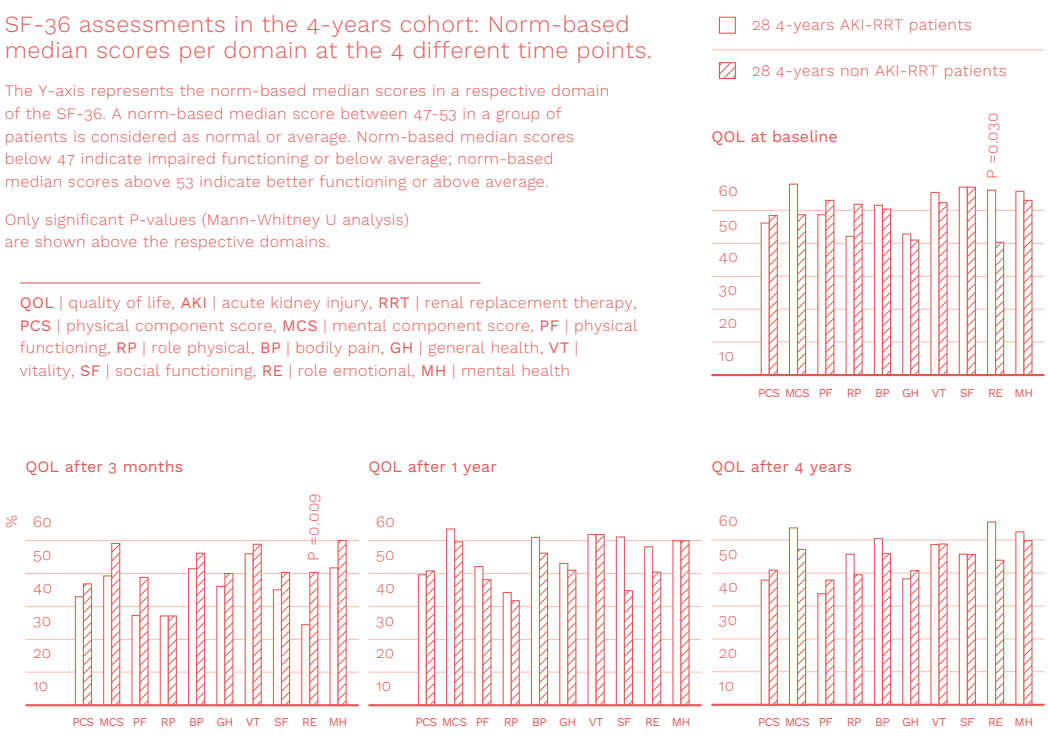


Table 2.

Persons who rated QOL, assessment of QOL, number of completed QOL surveys.

QOL | quality of life, N | number, AKI | acute kidney injury, RRT | renal replacement therapy

* All QOL surveys completed by face-to-face interviews
** All QOL surveys completed by regular mail
*** 46 QOL surveys completed; 32 by regular mail (69.6%) and 14 by phone interview (30.4%)
**** 94 QOL surveys completed; 67 by regular mail (71.3%) and 27 by phone interview (28.7%)
[a] 27 QOL surveys completed; 18 by regular mail (66.7%) and 9 by phone interview (33.3%
[b] 26 QOL surveys completed; 19 by regular mail (73.1%) and 7 by phone interview (26.9%)
[c] 28 QOL surveys completed; 14 by regular mail (50.0%) and 14 by phone interview (50.0%)
[d] 28 QOL surveys completed; 20 by regular mail (71.4%) and 8 by phone interview (28.6%)

	AKI-RRT	NON AKI-RRT	*P*	AKI-RRT	NON AKI-RRT	*P*	AKI-RRT	NON AKI-RRT	*P*	AKI-RRT	NON AKI-RRT	*P*
1-YEAR SURVIVORS		BASELINE			3 MONTHS			1 YEAR				
___	N=47 *	N=94 *		N=34 **	N=71 **		N=46 ***	N=94 ****				
PATIENT, *N (%)*	14 (29.8)	57 (60.6)	*0.001*	25 (73.5)	57 (80.3)	*0.434*	33 (71.7)	65 (69.1)	*0.753*			
PARTNER, *N (%)*	15 (31.9)	17 (18.1)	*0.065*	2 (5.9)	7 (9.9)	*0.496*	7 (15.2)	13 (13.8)	*0.826*			
SON/DAUGHTER, *N (%)*	8 (17.0)	9 (9.6)	*0.200*	3 (8.8)	4 (5.6)	*0.540*	1 (2.2)	8 (8.5)	*0.151*			
OTHER FAMILY, *N (%)*	4 (8.5)	5 (5.3)	*0.465*	0 (0)	0 (0)	*0.999*	1 (2.2)	2 (2.1)	*0.986*			
OTHERS, *N (%)*	6 (12.8)	6 (6.4)	*0.200*	4 (11.8)	4 (11.8)	*0.268*	4 (8.7)	6 (6.4)	*0.618*			
4-YEARS SURVIVORS		BASELINE			3 MONTHS			1 YEAR			4 YEARS	
___	N=28 *	N=27 *		N=21 **	N=23 **		N=27 [a]	N=26 [b]		N=28 [c]	N=28 [d]	
PATIENT, *N (%)*	8 (28.6)	18 (66.7)	*0.005*	17 (81.0)	17 (73.9)	*0.578*	22 (81.5)	22 (84.6)	*0.761*	24 (85.7)	21 (77.8)	*0.313*
PARTNER, *N (%)*	7 (25.0)	4 (14.8)	*0.345*	1 (4.8)	3 (13.0)	*0.340*	3 (11.1)	3 (11.5)	*0.961*	1 (3.6)	2 (7.4)	*0.553*
SON/DAUGHTER, *N (%)*	6 (21.4)	2 (7.4)	*0.140*	2 (9.5)	1 (4.3)	*0.496*	1 (3.7)	0 (0)	*0.322*	0 (0)	2 (7.4)	*0.150*
OTHER FAMILY, *N (%)*	3 (10.7)	3 (11.1)	*0.962*	0 (0)	1 (4.3)	*0.334*	0 (0)	0 (0)	*0.999*	0 (0)	2 (7.4)	*0.150*
OTHERS, *N (%)*	4 (14.3)	0 (0)	*0.041*	1 (4.8)	1 (4.3)	*0.947*	1 (3.7)	1 (3.4)	*0.978*	3 (10.7)	1 (3.7)	*0.299*

the mental components (Additional File-Fig. 2C). Changes in long-term QOL in the 4-years non AKI-RRT patients were less pronounced (Supplemental File-Fig. 2D).

The 4-years AKI-RRT patients showed a decrease in VAS after 3 months (63), and improvements after 1 (70) and 4 years (68) but without regain of the baseline level (70) (P=0.044). The 4-years non AKI-RRT patients had the same evolution but without significance (P=0.327).

Supplemental file 3 and additional files 4 illustrate in more detail the variability in EQ-5D and SF-36 over time.

Overall, long-term QOL remained under the baseline level for AKI-RRT and non AKI-RRT patients, and under the QOL of the average population.

3.6 ADDITIONAL QUESTIONS AFTER 1 YEAR AND 4 YEARS

One and 4 years after ICU discharge, most survivors lived independently, and only a minority stayed in a special care facility (Table 1). There were no major sleeping problems. One year and 4 years after ICU discharge, AKI-RRT patients had more bad memories than non AKI-RRT patients (17.4% vs 4.3%, P=0.010; 21.4% vs 3.8%, P=0.055). 81.8% of the 1-year AKI-RRT patients preferred to be readmitted to an ICU department in case of deterioration versus 83.0% of their 1-year matches (P=0.867). This number decreased to 71.4% for the 4-years AKI-RRT patients versus 84.6% for the 4-years non AKI-RRT patients (P=0.244).

4. Discussion

In this prospective single center matched cohort study concerning long-term outcomes and QOL of AKI-RRT patients, we found high mortality rates and lower QOL levels compared to the general population.

Similar to others, we found high hospital mortality (55%) in this cohort of critically ill AKI-RRT patients, with only moderate increase of mortality at longer follow-up (58% at 3 months, 61% at 1 year, 71% at 4 years) [4, 14, 15, 20, 36].

At hospital discharge and at long-term, a quarter of AKI-RRT hospital survivors were RRT dependent. These findings are similar to those reported in literature [37].

Long-term survival data would be meaningless without considering QOL. Remarkably, there was no difference in QOL at different time points between AKI-RRT patients and matched non AKI-RRT patients, although changes in QOL over time were less pronounced in the latter group. QOL decreased 3 months after ICU discharge compared to baseline, improved after 1 year, and stayed the same or improved slightly after 4 years, but still remained under baseline level.

The fact that long-term QOL had the same evolution over time in AKI-RRT and non AKI-RRT patients was quite surprising suggesting that the AKI-RRT component during critical illness did not have an important impact on long-term QOL. Others reported very similar findings, however, these studies reported only on QOL after 6 months, and in 1 study not all AKI patients received RRT, and some patients received RRT without AKI [20, 21].

The fact that AKI-RRT patients were more severely ill during their ICU stay compared to matched patients had no influence on QOL over the years. This is in accordance with the findings of Orwelius et al [38]. In a multicenter study they found that 6 months after ICU discharge, perceived QOL in sepsis patients did not differ from ICU survivors with other diagnoses, even though these sepsis patients were more severely ill, and had a longer ICU stay. Another study by Orwelius suggested that long-term QOL was mainly affected by co-morbidity [39]. In our study AKI-RRT and non AKI-RRT patients had a very comparable co-morbidity and medical history, which may explain the comparable long-term QOL between groups in our study. QOL was perceived as acceptable and both AKI-RRT and non AKI-RRT patients reported low dependence in daily life later on. The number of AKI-RRT and non AKI-RRT patients who agreed to undergo life-sustaining interventions again in case of deterioration remained high. However, QOL was lower

compared to that of the average population in both groups specifically in the more physical domains. This is in accordance with the findings of others [12-16, 20, 21].

Our study has several strengths. First, the matched cohort design demonstrates the real impact of AKI-RRT upon long-term QOL. This has not been evaluated thus far. Second, QOL was assessed with validated questionnaires at baseline, which allows for the only reliable evaluation of QOL over time without recall or selection bias [11, 40]. Third, the additional questions and VAS score allowed evaluation of the patients' perception of the ICU admission and the consequences of severe illness. Finally, most studies report QOL in AKI survivors as a short-term endpoint, while this study provides also data for a longer follow-up period. Strict time intervals of 3 months and 1 year after ICU discharge were respected in all patients. For long-term assessment of QOL, an arbitrary time point was chosen (August 2013) which was between 47-52 months after ICU discharge for all patients. Response rate was very high and only 3 patients were lost to-follow-up.

Some limitations should also be mentioned. First, single center data from a university hospital may not reflect general practice and may limit external validity of the data. Second, although 1-year and 4-years AKI-RRT patients were matched to non AKI-RRT patients based on 4 criteria, we cannot exclude that matched patients had a different profile compared to AKI-RRT patients. Third, the study cohort is relatively small and may lack of statistical power to detect differences among the QOL domains in our study patients. Fourth, medical decisions leading to ICU referral may have selected for patients with better prospects. Fifth, long-term QOL may also be modified by events happening to the patient after hospital discharge. These were not recorded in the present study.

5. Conclusions

We found high mortality rates in AKI-RRT patients. However, in long-term critically ill AKI-RRT survivors, QOL was comparable to matched long-term critically ill survivors without AKI-RRT, but lower than in the general population. The majority of AKI-RRT patients wanted to be readmitted to the ICU when needed, despite a higher severity of illness compared to matched non AKI-RRT patients, and despite the fact that one quarter had persistent dialysis dependency.

AUTHORS' CONTRIBUTION

SO and WDC acquired, analyzed and interpreted data. They also performed statistical analyses. They both were involved in drafting the manuscript, and revised it several times critically. DB, LA, AD, and RV revised the manuscript critically and helped with correct interpretation of data. JDC made a major contribution to the design of the study and interpretation of the data, and revised the manuscript critically. EH made a major contribution to the design of the study, helped and gave advice with the statistical analysis and with interpretation of data, and revised the manuscript critically. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' INFORMATION

DB and EH both have a Research Grant from the FWO, Brussels, Belgium.

ACKNOWLEDGEMENTS

The authors wishes to thank the study nurses Patrick Debaets, Patsy Priem, Jo Vandenbossche, and Daniella Van der Jeught for their tremendous help, motivation, and enthousiasm concerning inclusions, interviewing patients, and calling patients or relatives. The authors also thank Chris Danneels for his help in setting up the database.

REFERENCES

[1] Uchino S, Kellum JA, Bellomo R et al. Acute renal failure in critically ill patients. JAMA. 2005; 294: 813-8

[2] Hoste EA, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? Crit Care Med. 2008; 36 Suppl 4: 146-51

[3] Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RMH et al. Intensity of renal support in critically ill patients with acute kidney injury. New Engl J Med. 2008; 359:7-20

[4] Bellomo R, Cass A, Norton R, Gallagher M, Lo S, Su S, Cole L, Finfer S, McArthur C, McGuinness S et al. Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients. New Engl J Med. 2009; 361:1627-38

[5] Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int. 2009; 76:1089-97

[6] Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, Collins AJ. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009; 20:223-8

[7] Gammelager H, Christiansen CF, Johansen MB, Tonnesen E, Jespersen B, Sorensen HT. One-year mortality among Danish intensive care patients with acute kidney injury: a cohort study. Crit Care. 2012; 16:R124

[8] Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014; 371:58-66

[9] Mehlhron J, Freytag A, Schmidt K, Brunkhorst FM, Graf J, Troitzsch U et al. Rehabilitation interventions for postintesive care unit syndrome: a systematic review. Crit Care Med. 2014; 42: 1263-71

[10] Oeyen S, Vandijck D, Benoit D, Decruyenaere J; Annemans L, Hoste E. Long-term outcome after acute kidney injury in critically-ill patients. Acta Clin Belg. 2007; 62 Suppl 2: 337-40

[11] Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruynaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. 2010; 38: 2386-400

[12] Ahlstrom A, Tallgren M, Peltonen S, Rasanen P, Pettila V. Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Med. 2005; 31:1222-8

[13] Delannoy B, Floccard B, Thiolliere F, Kaaki M, Badet M, Rosselli S, Ber CE, Saez A, Flandreau G, Guerin C. Six-month outcome in acute kidney injury requiring renal replacement therapy in the ICU: a multicentre prospective study. Intensive Care Med. 2009; 35:1907-15

[14] Morgera S, Kraft AK, Siebert G, Luft FC, Neumayer HH. Long-term outcomes in acute renal failure patients treated with continuous renal replacement therapies. Am J Kidney Dis. 2002; 40:275-9

[15] Korkeila M, Ruokonen E, Takala J. Costs of care, long-term prognosis and quality of life in patients requiring renal replacement therapy during intensive care. Intensive Care Med. 2000; 26:1824-31

[16] Gopal I, Bhonagiri S, Ronco C, Bellomo R. Out of hospital outcome and quality of life in survivors of combined acute multiple organ and renal failure treated with continuous venovenous hemofiltration/ hemodiafiltration. Intensive Care Med. 1997; 23:766-72

[17] Abelha FJ, Botelho M, Fernandes V, Barros H. Outcome and quality of life of patients with acute kidney injury after major surgery. Nefrologia 2009; 29:404-14

[18] Maynard SE, Whittle J, Chelluri L, Arnold R. Quality of life and dialysis decisions in critically ill patients with acute renal failure. Intensive Care Med. 2003; 29:1589-93

[19] Morsch C, Thome FS, Balbinotto A, Guimaraes JF, Barros EG. Health-related quality of life and dialysis dependence in critically ill patient survivors of acute kidney injury. Ren Fail. 2011; 33:949-56

[20] Vaara ST, Pettila V, Reinikainen M, Kaukonen KM, Consortium FIC. Population-based incidence, mortality and quality of life in critically ill patients treated with renal replacement therapy: a nationwide retrospective cohort study in finnish intensive care units. Crit Care. 2012; 16: R13

[21] Hofhuis JG, van Stel HF, Schrijvers AJ, Rommes JH, Spronk PE. The effect of acute kidney injury on long-term health-related quality of life: a prospective follow-up study. Crit Care. 2013; 17:R17

[22] Noble JS, Simpson K, Allison ME. Long-term quality of life and hospital mortality in patients treated with intermittent or continuous hemodialysis for acute renal and respiratory failure. Ren Fail. 2006, 28:323-30

[23] Hamel MB, Phillips RS, Davis RB, Desbiens N, Connors AF, Jr., Teno JM, Wenger N, Lynn J, Wu AW, Fulkerson W. Outcomes and cost-effectiveness of initiating dialysis and continuing aggressive care in seriously ill hospitalized adults. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Ann Intern Med. 1997; 127:195-202

[24] De Corte W, Oeyen S, Annemans L, Benoit D, Dhondt A, Vanholder R, et al. Long-term outcome and quality of life in ICU patients with acute kidney injury treated with renal replacement therapy: a case control study. Intensive Care Med. 2014; 40 Suppl 1: 13

[25] Oeyen S, Benoit D, Annemans L, Decruyenaere J. Quality of life before, 3 months, and 1 year after ICU discharge. Crit Care Med. 2010; 38 Suppl December: P587

[26] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ et al. Strengthening the reporting of observational studies in epidemiology. Epidemiology. 2007; 18: 805-35

[27] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. (1987); 40:373-83.

[28] Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II. A severity of disease classification system. Crit Care Med. 1985; 13:818-29

[29] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996; 22:707-10

[30] Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M et al. Comparative performance of the CKD Epidemiology Collaboration (CKI-EPI) and the modification of diet in renal disease (MDRD) study equations for estimating GFR levels above 60 mL/min/1.73 m². Am J Kidney Dis. 2010; 56: 486-95

[31] Ware JE, Kosinski M, Bjorner JB, Turner-Bowler DM, Gandek B, Maruish ME. User's Manual for the SF-36v2® Health Survey. QualityMetric Incorporated, Lincoln, Rhode Island; 2007.

[32] Chrispin PS, Scotton H, Rogers J, Lloyd D, Ridley SA. Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. Anaesthesia. 1997; 52:15-23

[33] EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990; 16:199-208

[34] Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing It with the Sf-36 Health Survey Questionnaire. Qual Life Res. 1993; 2:169-80

[35] Angus DC, Carlet J, Brussels Roundtable P. Surviving intensive care: a report from the 2002 Brussels Roundtable. Intensive Care Med. 2003; 29:368-77

[36] Palevsky PM. Renal support in acute kidney injury--how much is enough? New Engl J Med. 2009; 361: 1699-701

[37] Wald R, McArthur E, Adhikari NK, Bagshaw SM, Burns KE, Garg AX et al. Changing incidence and outcomes following dialysis-requiring acute kidney injury among critically ill adults: A population-based cohort study. Am J Kidney Dis. 2015; 65: 870-7

[38] Orwelius L, Lobo C, Teixeira Pinto A, Carneiro A, Costa-Pereira A, Granja C. Sepsis patients do not differ in health-related quality of life compared with other ICU patients. Acta Anaesthesiol Scand. 2013; 57: 1201-5

[39] Orwelius L, Nordlund A, Nordlund P, Simonsson E, Backman C, Samuelsson A, Sjoberg F. Pre-existing disease: the most important factor for health related quality of life long-term after critical illness: a prospective, longitudinal, multicentre trial. Crit Care. 2010; 14: R67

[40] Joyce VR, Smith MW, Johansen KL, Unruh ML, Siroka AM, O'Connor TZ, Palevsky PM, Veteran Affairs/National Institutes of Health Acute Renal Failure Trial N. Health-related quality of life as a predictor of mortality among survivors of AKI. Clin J Am Soc Nephrol. 2012; 7:1063-70.

Table E1.

Variability of the EQ-5D at the different time points: Percentages and 95% confidence intervals* of patients with some or severe problems on the respective dimensions.

AKI | acute kidney injury, RRT | renal replacement therapy, CI | confidence interval

* The confidence interval was calculated according to DG Altman, D Machin, TN Bryant, M Gardner (2000). Statistics with confidence: Confidence intervals and statistical guidelines. BMJ Books

	BASELINE	3 MONTHS	1 YEAR	4 YEARS	*P*
47 1-YEAR AKI-RRT PATIENTS % (95% CI)					
MOBILITY	39.1 (26.4-53.5)	63.6 (46.6-77.8)	60.9 (46.5-73.6)		*0.045*
SELF-CARE	23.9 (13.9-37.9)	42.4 (27.2-59.2)	37.0 (24.5-51.4)		*0.190*
USUSAL ACTIVITIES	37.0 (24.5-51.4)	81.8 (65.6-91.4)	60.9 (46.5-73.6)		*<0.001*
PAIN/DISCOMFORT	45.7 (32.2-59.8)	75.8 (59.0-87.2)	54.3 (40.2-67.8)		*0.013*
ANXIETY/DEPRESSION	30.4 (19.1-44.8)	60.6 (43.7-75.3)	30.4 (19.1-44.8)		*0 (0)*
94 1-YEAR NON AKI-RRT PATIENTS % (95% CI)					
MOBILITY	37.2 (28.1-47.3)	54.9 (43.4-66.0)	55.4 (45.3-65.2)		*0.021*
SELF-CARE	24.5 (16.9-34.0)	40.8 (30.2-52.5)	38.0 (28.8-48.3)		*0.050*
USUSAL ACTIVITIES	46.8 (37.0-56.8)	81.7 (71.2-89.0)	66.3 (56.2-75.1)		*<0.001*
PAIN/DISCOMFORT	51.1 (41.1-60.9)	70.4 (59.0-79.8)	63.0 (52.8-72.2)		*0.035*
ANXIETY/DEPRESSION	40.4 (31.1-50.5)	39.4 (28.9-51.1)	41.3 (31.8-51.5)		*0.971*
28 4-YEARS AKI-RRT PATIENTS % (95% CI)					
MOBILITY	25.9 (13.2-44.7)	61.9 (40.9-79.2)	59.3 (40.7-75.5)	50.0 (32.6-67.4)	*0.040*
SELF-CARE	14.8 (5.9-32.5)	47.6 (28.3-67.6)	33.3 (18.6-52.2)	25.9 (13.2-44.7)	*0.090*
USUSAL ACTIVITIES	25.9 (13.2-44.7)	81.0 (60.0-92.3)	55.6 (37.3-72.4)	70.4 (51.5-84.1)	*<0.001*
PAIN/DISCOMFORT	48.1 (30.7-66.0)	71.4 (50.0-86.2)	59.3 (40.7-75.5)	55.6 (37.3-72.4)	*0.439*
ANXIETY/DEPRESSION	29.6 (15.9-48.5)	61.9 (40.9-79.2)	25.9 (13.2-44.7)	29.6 (15.9-48.5)	*0.040*
28 4-YEARS NON AKI-RRT PATIENTS % (95% CI)					
MOBILITY	18.5 (8.2-36.7)	39.1 (22.2-59.2)	41.7 (24.5-61.2)	60.7 (42.4-76.4)	*0.017*
SELF-CARE	11.1 (3.9-28.1)	21.7 (9.7-41.9)	25.0 (12.0-44.9)	28.6 (15.3-47.1)	*0.436*
USUSAL ACTIVITIES	29.6 (15.9-48.5)	47.8 (29.2-67.0)	70.8 (50.8-85.1)	64.3 (45.8-79.3)	*0.014*
PAIN/DISCOMFORT	37.0 (21.5-55.8)	26.1 (12.5-46.5)	45.8 (27.9-64.9)	53.6 (35.8-70.5)	*0.227*
ANXIETY/DEPRESSION	51.9 (34.0-69.3)	17.4 (7.0-37.1)	25.0 (12.0-44.9)	32.1 (17.9-50.7)	*0.054*

Table E2.

Variability of the SF-36 norm-based scores at the different time points: median and interquartile ranges.

AKI | acute kidney injury, RRT | renal replacement therapy, IQR | interquartile range (25%-75%), PCS | physical component score, MCS | mental component score

	BASELINE	3 MONTHS	1 YEAR	4 YEARS	*P*
47 1-YEAR AKI-RRT PATIENTS MEDIAN (IQR)					
PCS	41.7 (28.5-54.2)	30.7 (25.1-40.4)	38.3 (27.7-47.4)		*0.003*
MCS	53.8 (38.9-61.6)	39.5 (29.3-47.2)	53.3 (39.2-58.6)		*0.014*
PHYSICAL FUNCTIONING	44.4 (29.1-53.4)	27.6 (19.2-39.1)	40.2 (26.5-46.5)		*<0.001*
ROLE PHYSICAL	34.8 (22.6-56.9)	27.5 (17.7-29.9)	34.8 (25.0-45.8)		*<0.001*
BODILY PAIN	62.1 (37.2-62.1)	39.7 (29.2-50.9)	46.5 (37.2-62.1)		*0.015*
GENERAL HEALTH	40.1 (30.5-48.2)	36.3 (31.1-41.0)	41.0 (30.5-50.6)		*0.078*
VITALITY	55.2 (42.7-61.5)	45.8 (39.6-50.5)	50.5 (41.9-59.1)		*0.041*
SOCIAL FUNCTIONING	51.4 (35.0-56.8)	35.0 (24.1-40.5)	45.9 (29.6-56.8)		*0.005*
ROLE EMOTIONAL	55.9 (40.3-55.9)	28.7 (20.9-38.4)	48.1 (32.6-55.9)		*<0.001*
MENTAL HEALTH	50.0 (33.1-61.3)	41.6 (30.3-50.0)	50.0 (40.2-58.4)		*0.022*
94 1-YEAR NON AKI-RRT PATIENTS MEDIAN (IQR)					
PCS	39.4 (29.1-49.6)	31.3 (26.3-43.2)	36.6 (26.0-46.4)		*0.007*
MCS	48.0 (37.5-55.7)	47.3 (31.6-54.9)	47.8 (34.8-54.0)		*0.759*
PHYSICAL FUNCTIONING	40.2 (23.4-53.4)	31.8 (21.3-44.4)	33.9 (22.3-48.6)		*0.001*
ROLE PHYSICAL	34.8 (22.6-56.9)	27.5 (17.7-37.3)	32.4 (23.2-42.2)		*0.059*
BODILY PAIN	46.5 (33.3-62.1)	39.5 (29.2-50.5)	41.6 (29.2-55.4)		*0.008*
GENERAL HEALTH	37.7 (30.5-50.6)	40.1 (31.1-45.8)	37.7 (30.5-45.8)		*0.871*
VITALITY	49.0 (36.5-58.3)	49.0 (39.6-55.2)	49.0 (36.5-58.3)		*0.896*
SOCIAL FUNCTIONING	48.7 (35.0-56.8)	35.0 (24.1-45.9)	35.0 (24.1-51.4)		*<0.001*
ROLE EMOTIONAL	55.9 (31.6-55.9)	38.4 (20.9-55.9)	44.2 (24.8-55.9)		*0.410*
MENTAL HEALTH	47.2 (33.1-58.4)	50.0 (34.5-55.7)	47.2 (34.5-55.6)		*0.562*
28 4-YEARS AKI-RRT PATIENTS MEDIAN (IQR)					
PCS	46.1 (38.7-53.7)	33.2 (26.0-40.4)	39.8 (31.6-46.7)	38.1 (31.6-47.1)	*0.007*
MCS	57.6 (42.8-62.3)	39.5 (29.3-47.1)	53.5 (40.9-61.6)	53.9 (42.4-60.3)	*0.010*
PHYSICAL FUNCTIONING	48.6 (36.5-57.0)	27.6 (18.1-43.4)	42.3 (29.7-48.6)	33.9 (29.7-40.2)	*<0.001*
ROLE PHYSICAL	42.2 (27.5-56.9)	27.5 (17.7-31.8)	34.8 (27.5-47.1)	45.9 (27.5-56.9)	*<0.001*
BODILY PAIN	51.1 (38.2-62.1)	41.8 (30.1-50.9)	51.1 (41.8-62.1)	50.7 (34.4-62.1)	*0.178*
GENERAL HEALTH	42.9 (30.3-47.9)	36.3 (32.9-42.9)	43.4 (36.3-50.6)	38.2 (32.9-48.0)	*0.093*
VITALITY	55.2 (43.5-64.6)	45.8 (42.7-50.5)	52.1 (45.8-61.5)	49.0 (45.8-58.3)	*0.037*
SOCIAL FUNCTIONING	56.8 (40.5-56.8)	35.0 (26.9-40.5)	51.4 (35.0-56.8)	45.9 (35.0-56.8)	*0.101*
ROLE EMOTIONAL	55.9 (50.0-55.9)	24.8 (9.2-38.4)	48.1 (32.6-55.9)	55.9 (20.9-55.9)	*0.001*
MENTAL HEALTH	55.6 (33.1-64.1)	41.6 (33.1-51.4)	50.0 (41.6-61.3)	52.8 (41.6-58.5)	*0.188*
28 4-YEARS NON AKI-RRT PATIENTS MEDIAN (IQR)					
PCS	48.4 (36.3-57.0)	37.1 (26.1-45.5)	40.8 (27.9-46.5)	41.0 (32.1-52.6)	*0.358*
MCS	48.6 (34.3-57.6)	48.9 (37.2-54.8)	49.7 (40.6-54.7)	47.0 (37.4-55.5)	*0.913*
PHYSICAL FUNCTIONING	52.8 (40.2-54.9)	39.1 (19.2-44.4)	38.1 (22.3-48.6)	38.1 (25.5-48.6)	*<0.001*
ROLE PHYSICAL	52.0 (17.7-56.9)	27.5 (25.0-39.7)	32.4 (25.0-39.7)	39.7 (25.0-47.1)	*0.158*
BODILY PAIN	50.3 (41.2-62.1)	46.1 (37.2-55.4)	46.1 (36.1-62.1)	46.1 (37.2-62.1)	*0.489*
GENERAL HEALTH	41.0 (35.3-55.3)	40.1 (29.8-49.4)	41.0 (35.3-48.8)	41.0 (34.7-53.5)	*0.577*
VITALITY	52.1 (42.7-58.3)	49.0 (39.6-58.3)	52.1 (39.6-58.3)	49.0 (42.7-55.2)	*0.403*
SOCIAL FUNCTIONING	56.8 (35.0-56.8)	40.5 (24.1-51.4)	35.0 (22.8-52.8)	45.9 (24.1-56.8)	*0.058*
ROLE EMOTIONAL	40.3 (20.9-55.9)	40.3 (28.7-55.9)	40.3 (24.8-55.9)	44.2 (24.8-55.9)	*0.071*
MENTAL HEALTH	52.8 (35.9-58.4)	50.0 (37.3-58.5)	50.0 (37.3-58.5)	50.0 (41.6-52.8)	*0.962*

Fig. E1.

EQ-5D assessments over time: Percentages of patients with some or severe problems per dimension.

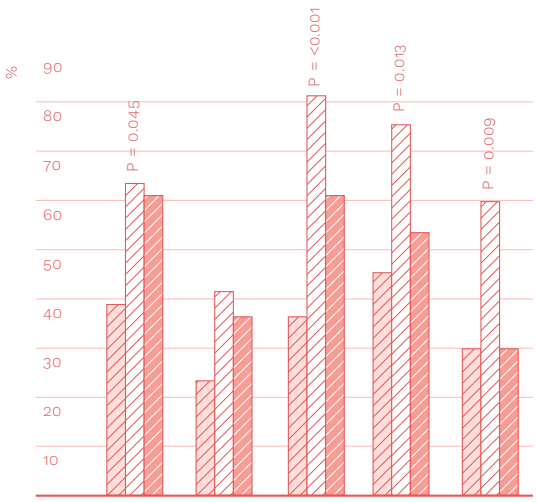
The X-axis represents the different dimensions of the EQ-5D.
The Y-axis represents the percentages (%) of patients with some or severe problems in a respective dimension.

Only significant P-values (Chi Square test) are shown above the respective dimensions.

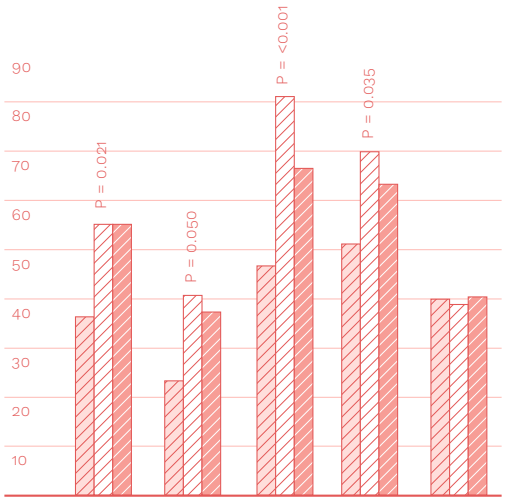
QOL at baseline
QOL after 3 months
QOL after 1 year
QOL after 4 years

QOL | quality of life, **AKI** | acute kidney injury, **RRT** | renal replacement therapy

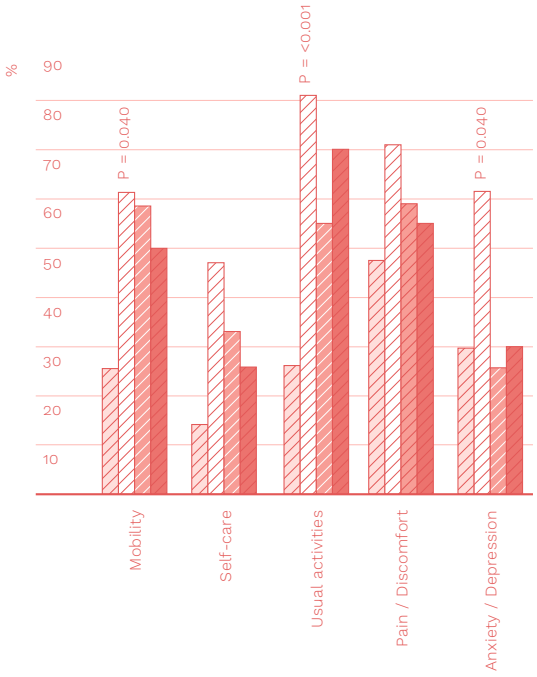
E1.a 47 1-year AKI-RRT patients



E1.b 94 1-year non AKI-RRT patients



E1.c 28 4-years AKI-RRT patients



E1.d 28 4-years non AKI-RRT patient

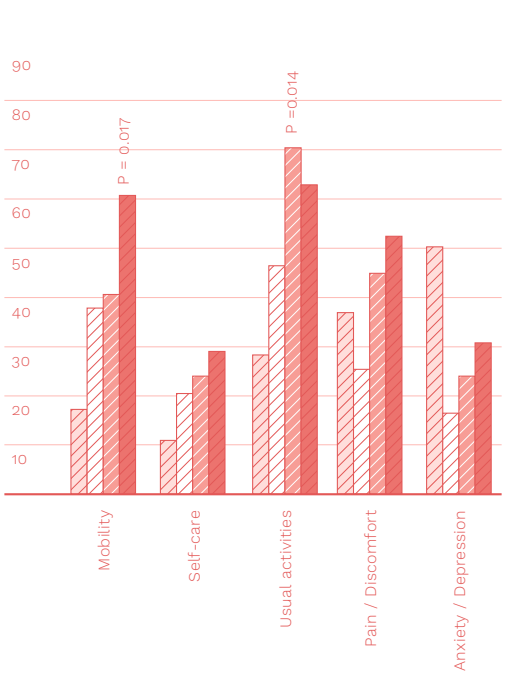


Fig. E2.

SF-36 assessments over time: Norm-based median scores per domain.

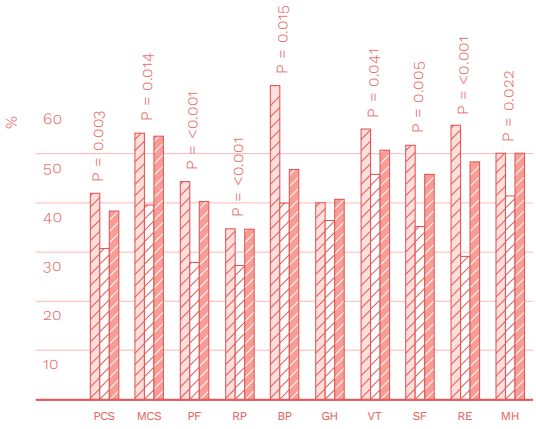
The X-axis represents the different domains of the SF-36. The Y-axis represents the norm-based median scores in a respective domain of the SF-36. A norm-based median score between 47-53 in a group of patients is considered as normal or average. Norm-based median scores below 47 indicate impaired functioning or below average; norm-based median scores above 53 indicate better functioning or above average.

Only significant P-values (Friedman test) are shown above the respective domains.

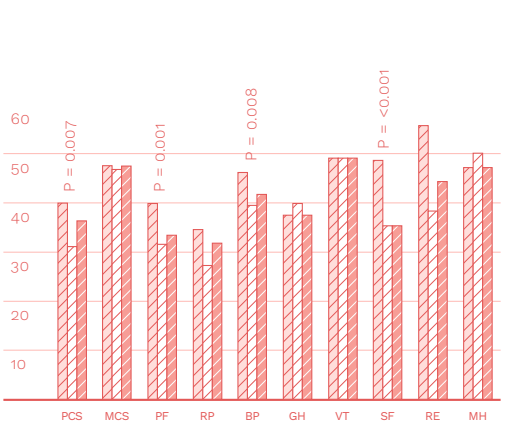
QOL | quality of life, AKI | acute kidney injury, RRT | renal replacement therapy, PCS | physical component score, MCS | mental component score, PF | physical functioning, RP | role physical, BP | bodily pain, GH | general health, VT | vitality, SF | social functioning, RE | role emotional, MH | mental health

QOL at baseline
QOL after 3 months
QOL after 1 year
QOL after 4 years

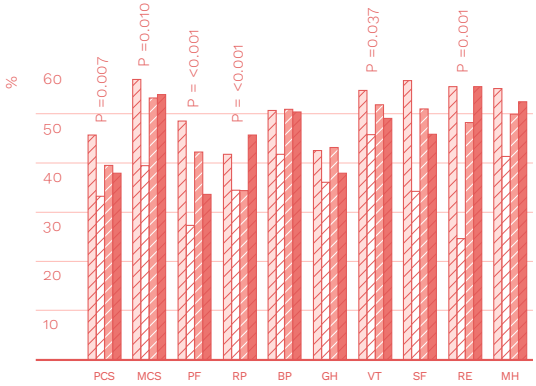
E2.a 47 1-year AKI-RRT patients



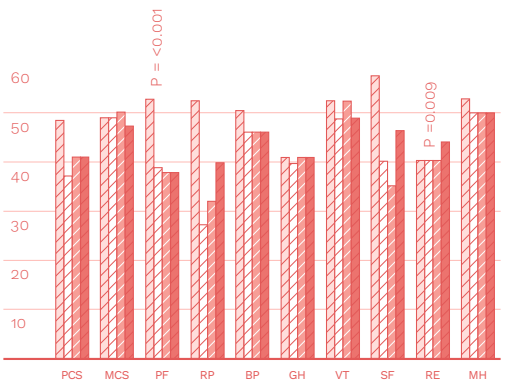
E2.b 94 1-year non AKI-RRT patients



E2.c 28 4-years AKI-RRT patients



E2.d 28 4-years non AKI-RRT patient



7

1. Major findings

The overall aim of this doctoral thesis was to: 1) describe the epidemiology of critically ill patients with AKI-RRT, 2) to explore timing of initiation of RRT in these patients by studying some "conventional" indications of initiation of RRT and evaluating their possible impact on outcome, 3) assess short- and long-term patient and kidney outcomes in this specific cohort of patients and 4) investigate long-term quality of life in these patients. These objectives were addressed by four studies.

The first objective was to describe the epidemiology of critically ill patients with AKI-RRT. As an epidemiological research project this objective was addressed in all four presented studies each highlighting specific endpoints and outcome measures. In study I and II mortality was the main clinical outcome measure. We found that almost 60% of the patients died during hospital stay. In patients with SLA, these mortality rates further increased (>80% ICU mortality). In study III we further focused on long-term patient and kidney outcome and highlighted the concept of composite endpoints. An additional mortality rate of 10% per year was reported in patients discharged from the hospital. The second objective was to investigate some "classical" indications of initiation of RRT in ICU patients with AKI-RRT and to evaluate possible associations with outcome. This was addressed by a retrospective study:

Study I investigated whether serum urea cut-off concentrations for initiation of RRT had a possible predictive value for short-term mortality. On a Vancouver meeting, members of the Acute Kidney Injury Network formulated indications to initiate RRT. Regarding serum urea concentration cut-offs they recommended a BUN>76 mg/dl as a relative and a BUN>100 mg/dl an absolute indication to initiate RRT [1]. Further, the 2012 KDIGO guidelines on AKI depicted solute control (BUN) as a potential application for initiation of RRT but only when considering the broader clinical context, the presence of conditions that can be modified with RRT and trends of laboratory tests [2]. We found that serum urea concentration cut-offs at time of initiation of RRT, as they have been used from the early days of acute RRT have no predicted value for hospital mortality in severely ill patients with AKI.

The third objective was to assess the short and long-term patient and kidney outcomes and their determinants in ICU patients with AKI-RRT. This topic was addressed by a retrospective study (study II) and an observational prospective study (Study III):

Study II extensively focused on a second well-known classical indication for initiation of RRT in critically ill patients with AKI: severe lactic acidosis. First we described the epidemiology of this condition. Second, we investigated possible factors that may have influenced short-term outcome. SLA was present in about one third of AKI-RRT patients and was associated with an ICU mortality rate of more than 80%. We demonstrated that the administration of RRT –irrespective from RRT modality– was associated with an increase in serum pH and a decrease of serum lactate concentration in most patients. In addition, serum lactate concentration at initiation of RRT was not able to discriminate between survivors and non-survivors. This study suggests that initiation of RRT in these patients may act as a bridge that buys time to treat the underlying cause of the acidosis.

Study III evaluated long-term patient and kidney outcomes in AKI-RRT patients. We also evaluated possible determinants of outcome in these patients. Long-term survival after AKI-RRT was poor and associated with age and clinical status at initiation of RRT. Renal recovery was limited and deficient recovery was associated with CKD and diabetes. Evolution towards ESKD was more frequently seen in patients with acute on chronic disease. The majority of patients classified positive for MAKE.

The fourth objective was to evaluate long-term quality of life in AKI-RRT patients after discharge from ICU. This topic was addressed by a prospective matched cohort study:

Study IV described the long-term quality of life in AKI-RRT patients. The cohort described in this study is a subgroup of a prospective observational cohort [3]. Long-term quality of life was impaired compared to the general population but was not different from that of ICU survivors without AKI. Impaired QOL was predominantly driven by impairment in physical domains rather than mental domains.

2. Interpretation of the findings

2.1 OBJECTIVE 1 EPIDEMIOLOGY OF CRITICALLY ILL PATIENTS WITH AKI-RRT

Our 8-year analysis of more than 23,000 first ICU admissions demonstrated that AKI-RRT occurred in 5.5% of patients admitted to the ICU. This incidence is in line with the BEST kidney trial reporting an AKI-RRT incidence of 4.2% but lower than the AKI-EPI study and the study by Nisula (13.5% and 10.2%, respectively) [4-6]. Differences in baseline characteristics of the patients with increased occurrence of AKI and differences in timing of initiation of RRT may explain these differences [7].

In our study cohort, median age was 65 years, two-third of the patients were male. Almost one third of the patients had diabetes and almost 40% of the patients had a baseline CKD stage ≥3. Patients with AKI-RRT were very severely ill as depicted by the median SAPS II score of 63. ICU mortality was 54.6% and increased to 72.1% at three years. Older age and increased severity of illness during ICU stay were associated with long-term mortality.

2.2 OBJECTIVE 2 TIMING OF INITIATION OF RRT IN CRITICALLY ILL PATIENTS WITH AKI-RRT

2.2.1. How to define timing? Whether timing of initiation of RRT influences outcome in AKI-RRT patients remains a matter of debate [8]. Timing of initiation of RRT is puzzling, mainly because of the lack of a uniform definition of “early” versus “late”. As a consequence, clinical outcomes related to timing of initiation of RRT are influenced by how timing is defined. Starting dialysis in AKI patients may be based on traditional indications such as acidosis, electrolyte disorders like hyperkalemia, uremic complications (nowadays rarely seen uremic encephalopathy or uremic pericarditis) but clinical parameters such as UO and fluid overload, AKI severity stage or time from ICU admission. The present work evaluated several of these criteria of initiation of RRT.

2.2.2. Timing of initiation of RRT: definition based on biomarkers For years dialysis was reserved as a treatment for uremic symptoms in patients with AKI. In 1953 Teschan introduced the concept of “prophylactic dialysis” meaning RRT applied before the appearance for uremic symptoms [9]. Until recently the discussion was about which serum urea threshold should be used to optimize outcome after AKI. As a consequence timing was defined as “early” versus “late” with respect to a serum urea threshold concentration. Study I extensively focused on the possible association between different serum urea cut-offs and mortality. We demonstrated that serum urea concentration and serum urea cut-offs for initiation of RRT as described in literature had no predictive value for short-term hospital mortality in critically ill patients with AKI-RRT. Our findings were more recently confirmed by a systematic review by Ostermann et al [10]. They concluded that serum urea

concentration could not adequately define the optimal indication and time of initiation of RRT. More recently a prospective multicenter observational study confirmed these findings [11]. Consequently, the concept of "early" versus "late" timing of initiation of RRT based on historical serum urea cut-off concentrations does not make sense. This is mainly because the use of such a surrogate marker of kidney function is highly problematic due to the fact that it is not renal specific. The biological rationale that urea is a good biomarker for assessing the severity and duration of AKI is weak. Serum urea is determined by many other variables that have no relation to kidney function. It is formed by the hepatic metabolism of amino acids and excreted primarily by glomerular filtration. Serum concentrations may vary as a result of changes in urea production and tubular urea reabsorption without changes in GFR. Both increased metabolism (i.e. in the context of gastrointestinal bleeding, enhanced tissue breakdown or high protein diet) and increased tubular reabsorption during hypovolemic states can lead to increased serum urea levels without changes in renal function [10-12]. We want to highlight the fact that we used the RIFLE classification in Study I. RRT was not included in that score (see Table 2 p. 82). The more recent KDIGO classification for AKI classifies the administration of RRT as AKI stage 3. The different classification systems for AKI are presented in Table 1 (CHAPTER 1 Introduction).

2.2.3. Timing of initiation of RRT: definition based on life-threatening indications According to the KDIGO guidelines, another – more decisive – indication for initiation of RRT is the condition of severe and therefore possibly life-threatening acidosis. Intuitively this seems a plausible indication for initiation of RRT. However, evidence supporting this advice is scarce. Study II wanted to update the literature concerning this topic. We found that SLA was a frequent finding in critically ill patients associated with high mortality. However, in patients with SLA, serum lactate concentration at initiation of RRT could not discriminate between survivors and non-survivors. We can formulate several explanations for this finding. First, RRT does not treat the underlying disease. It only can provide restoration of homeostatic equilibrium [13]. Second, whether lactate clearance during RRT could sufficiently impact serum lactate remains a matter of debate [14, 15]. A decrease in serum lactate can be the result of the natural (beneficial) course of the underlying disease, rather than an increased clearance due to RRT. In conclusion, timing of initiation of RRT based on serum lactate concentration in patients with SLA is not associated with outcome. In conclusion timing of initiation of RRT based on serum lactate concentration in patients with SLA is not associated with outcome. As such, we suggest not to withhold RRT in these very severely ill patients as this intervention may create a window of opportunity for correcting acidosis and restoring homeostasis enabling specific therapeutic measures to treat the underlying disease. However, this hypothesis needs further research.

2.2.4. Timing of initiation of RRT: temporal definition Another used definition of timing of initiation of RRT is based on a temporal approach indicating several arbitrarily chosen time intervals: time from hospital or ICU admission to initiation of RRT. The BEST Kidney investigators performed a prospective multinational observational study on 1238 patients evaluating the timing of RRT stratified into "early" and "late" by biochemical parameters and temporal criteria [16]. Patients were stratified into early RRT (defined by start within 2 days), delayed RRT (defined by start between 2 and 5 days) and late RRT (defined by start after 5 days from ICU admission). Late RRT was associated with a significantly higher crude mortality as compared with delayed or early RRT (72.8% versus 62.1%, versus 58.9%;P<0.001). After adjustment for covariates late RRT remained independently associated with hospital mortality and was also associated with an increased duration of RRT At hospital discharge, there was no difference in dialysis dependency. Despite the better outcome in favor of early RRT, a major drawback of a temporal definition is that it indicates an arbitrarily chosen time interval. It finds origin in the initiation of RRT in CKD patients inevitably evolving towards RRT, but cannot be very easily managed in AKI patients in which

dialysis may be avoided [17]. For example, it is difficult to discriminate those patients in the "late" group who might have had criteria for RRT early in a timely fashion. In conclusion, whatever temporal criteria are used to define early versus late RRT, it is apparent that what may be early for one patient could be late for another patient depending on the patient's comorbidity and clinical course [18].

2.2.5. Timing of initiation of RRT: definition based on AKI stage Timing of initiation of RRT defined on quantitative data defining severity of AKI, rather than on a temporal definition has major potential advantages. The definition is based on the actual pathophysiologic course of the disease, rather than driven by a surrogate marker or an arbitrary temporal definition. Therefore, when investigating the concept of timing of initiation of RRT we defined in study III "early" versus "late" initiation of RRT based on AKI stage. AKI stage 1 and 2 were defined as "early", stage 3 was defined as "late". However, in study III we found no association between timing of initiation of RRT and outcome. Our findings were confirmed by the recently published multicenter AKIKI trial by Gaudry et al [19]. Early was defined as initiation of RRT within 6 hours after documentation of AKI stage 3 of KDIGO classification. Similarly, all RRT modalities were used (IHD, CRRT, SLEDD). However, patients with life-threatening complications were excluded in the AKIKI trial making "late" initiation of RRT less risky. The monocentric ELAIN study by Zarbock et al showed a survival benefit for early initiation based on KDIGO stage ("early" means AKI KDIGO stage II, "late" means AKI KDIGO stage III) [20]. Early was defined as initiation of RRT at stage 2 of the KDIGO classification within 8 hours. CRRT was the only modality used. These studies illustrate how complex the impact of timing on outcome is. Differences between these studies were the definition of early and late initiation, but also modalities used (CRRT in ELAIN versus all modalities in the other studies) and study design (single center observation (ELAIN) versus multicenter studies). Some shortcomings inherent to AKI staging classifications need to be made. First, AKI staging is mainly based on evolution in serum creatinine concentrations and/or UO. Registration of these data may be problematic. Baseline sCr is often lacking or does not reflect 'true baseline sCr". Furthermore, sCr levels depend on renal function but also on nonrenal factors like age, muscle percentage of body weight and volume of distribution [21]. Fluid administration is common in the management of of critically ill patients. However, it may lead to fluid accumulation and result in an increase in total body weight of 10 -15% [22]. This may result in an increase in the volume of distribution of sCr. As a consequence, the severity of AKI may be underestimated in critically ill patients with a positive fluid balance. In addition, the diagnosis of AKI, based on sCr concentration may be delayed. Macedo et al developed a formula to correct for fluid balance. Serum creatinine values were adjusted using a correction factor based on the hospital admission weight and the daily fluid balance [21]. However this approach remains controversial as it lacks a clear physiological basis and fails to account for the actual kinetics of creatinine excretion [23]. Further, significant decreases in GFR are not always reflected by a major increase in serum creatinine levels hampering adequate AKI staging. Significant decreases in GFR are not always reflected by a major increase in serum creatinine levels hampering adequate AKI staging [21]. In addition laboratory techniques may also have an influence on the actual serum creatinine [23]. Finally, the RIFLE and AKIN classifications are scoring systems which were developed to grade prognosis of AKI but they were never intended to predict the need for RRT. For example, by definition AKI stage 3 implies RRT [2, 24].

2.2.6. Timing of initiation of RRT: definition based on clinical parameters Decision-making for initiation of RRT is also often based on clinical parameters like urine output and fluid overload. The usefulness of urine criteria for the definition of AKI has been debated widely but there is an increasing evidence that a UO of <500-600 mL/24h should be viewed as an ominous sign [25, 26]. In addition, oliguria is closely correlated with fluid accumulation. Recent data suggest that fluid overload of >10% of body weight is an independent risk factor for mortality in AKI

[27]. Consequently, it may be appropriate to consider starting RRT prior to fluid accumulation. Several studies found an association between decreased UO and mortality. In a retrospective study of critically ill patients with AKI, Ostermann found that oligoanuria (UO <400ml/24 h) was associated with ICU mortality [28]. In addition two small nonrandomized studies in cardiac surgery patients conducted by Demirkilic et al and Elahi et al demonstrated a survival benefit in case of early initiation of RRT based on UO criteria [29, 30]. Further, Sugahara et al conducted a small and monocentric RCT in 28 cardiac surgery patients [31]. Initiation of RRT was based on UO. Early was defined as a UO of <30 ml/h for three consecutive hours or daily UO of ≤ 750ml. Early initiation of RRT was associated with better 14-day survival in this specific cohort of patients. Interestingly, sCr levels at initiation of RRT did not significantly differ between both groups. In a recent prospective multicenter observational study Bagshaw et al demonstrated a significant association between mortality and UO prior to initiation of RRT [11]. Study III showed an inverse association between oliguria and renal recovery in univariate analysis. However, in multivariate analysis, no association could be demonstrated.

In conclusion, the timing of initiation of RRT remains controversial. Two meta-analyses showed that early initiation of RRT was associated with better outcome. Seabra et al concluded that early initiation of RRT was associated with a 28% mortality risk reduction. However this finding was largely based on data from retrospective trials [32]. Similarly, Karvellas et al reported an improvement in 28-day mortality with early RRT. However, a subgroup analysis of the included RCTs could not confirm this survival benefit [33]. These findings were not confirmed in two recent meta-analyses. A systematic review performed by Wierstra et al could not demonstrate an association between early initiation of RRT and outcome [34]. A systematic review and meta-analysis by Xu et al concluded that "early" RRT in one study might be considered as "late" in another study [35]. They included 6 RCTs and reported an equal number of definitions of "early" and "late" timing. So no firm statements could be made concerning the concept of timing of initiation of RRT.

Up to date it is practically impossible to predict which patient will benefit from RRT, and which patient will spontaneously recover from AKI without need of RRT [6]. Whether timing of initiation of RRT should be measured from ICU admission, from the moment of diagnosis of severe AKI, or using arbitrary thresholds of traditional or new biomarkers remains unclear. Intuitively early initiation of RRT seems attractive because of potential benefits attributable to more rapid metabolic and uremic control, better management of fluid overload and the prevention of organ injury following acidemia [36]. Pending further clarification, the decision to start RRT should be based on trends in the general severity of illness, presence of oliguria and fluid overload, the number and types of failed non-renal organs and the risk of further organ failure whether the patient is recovering of deteriorating [8].

2.3 OBJECTIVE 3 PATIENT AND KIDNEY OUTCOMES AND THEIR DETERMINANTS IN AKI-RRT PATIENTS

2.3.1. Short- and long-term mortality

We found that AKI-RRT was associated with adverse outcomes. Mortality rates in our cohort were high, with almost 60% of the patients dying during their hospital stay. These rates were comparable to the data presented by Ostermann et al (56.8%) and Uchino et al (60.0%), but higher than in studies by Nisula et al (25.6%), and Mehta et al (37.0%) [4, 6, 10, 37]. In a multicenter study on more than 15,000 patients Srisawat et al reported an overall hospital mortality of 27.0% [38]. Recently Ympa et al performed a systematic review exploring short-term mortality rates in critically ill patients with AKI [39]. They included publications between 1956 and 2003. Crude mortality rates were about 50%. The authors reported a wide variation in the mortality rates among included studies, but could not demonstrate an improved outcome over time. Possible explanations are differences in definitions of AKI or in case-mix (medical

versus surgical ICUs, increasing age of the patients over time). Inclusion criteria and patient group characteristics may differ among studies. For example, in patients with SLA we reported an ICU mortality of 83.6%. Further, differences in management among centers and over time may play a role. Similarly, Srisawat et al found a wide variety in hospital mortality rates across.

Illness in ICU patients focused on conventionally accepted short-term outcomes such as mortality at day 30, or ICU and hospital discharge. However, over the years the insight grew that these endpoints may underestimate the true burden of disease. So in modern-day ICU care, we should aim for more relevant endpoints such as long-term mortality (90 days, 6 months, one-year). The current project extensively addresses these long-term outcome measures. Next to the high hospital mortality rate, an additional mortality rate of 10% per year of the hospital survivors was reported in the years following discharge. This finding reflects the impact of AKI-RRT on long-term survival after ICU discharge. Again, these data are in line with current evidence in literature. The RENAL study reported a 44.7% mortality rate three months after initiation of RRT [40]. To avoid the selection bias inherent to hospital-based studies Bagshaw and co-workers set up a population-based study describing long-term outcomes in patients with AKI-RRT. They reported a 1-year mortality of 63.8% [41]. Korkeila et al reported 65.0% mortality at 5 years in a mixed surgical and medical Finnish ICU population with AKI without pre-existing renal failure [42]. Ahlström et al confirmed these findings in a cross-sectional cohort study on patients from a medical-surgical ICU and acute dialysis unit with a 5 years mortality of 70% [43]. We could identify several determinants of long-term outcome. Advanced age and conditions depicting the severity of illness during ICU stay: hemodynamic instability, administration of vasoactive medication, need for mechanical ventilation and a positive fluid balance were associated with long-term mortality. These findings confirm previous research [6, 44]. Interestingly, our research highlights the fact that an ICU admission complicated with an AKI-RRT episode is independently associated with mortality and has a long-lasting impact in these patients. These findings support the recently emerged paradigm shift that patients actually die of AKI instead of with AKI. In the past, the statement that patients died with AKI and not from AKI was widely accepted. AKI, and by extension AKI-RRT, was often considered a surrogate marker for severity of illness. In critically ill patients, AKI often developed in the course of another disease, e.g. sepsis or trauma. Patient mortality was considered a consequence of this underlying disease [45].

In study III, CRRT as initial RRT modality was associated with adverse long-term patient outcome. This finding must be interpreted with caution as the study was not designed to investigate differences in outcomes based on RRT modality. In addition, our institution tends to initiate CRRT in patients with hemodynamic instability. When a patient's condition improves, the modality is switched to SLEDD or IHD. So, in our cohort of patients, RRT modality acts a surrogate marker for severity of illness and may therefore have biased our findings. Either way, the optimal RRT modality remains a controversial issue. A recent study by Truche et al concluded that RRT modality had limited influence on patient and kidney outcome at 30 days and 6 months. CRRT was beneficial in patients with a positive fluid balance but was associated with adverse outcome in patients with stable hemodynamics [46]. A meta-analysis performed by Bagshaw et al could not demonstrate an association between RRT modality and mortality or renal recovery [41].

2.3.2. Renal recovery and dialysis dependency Until recently, it was widely accepted that kidney function of most patients surviving AKI fully recovers [47]. However, several studies have demonstrated the link between AKI, CKD and ESKD [48]. Despite the lack of a standard definition, the term "renal recovery" is widely used and is usually interpreted as independency of RRT [49]. However, renal recovery encompasses a varying range from full renal recovery to incomplete renal recovery close to the limit of dialysis dependency.

Study III extensively focuses on the concept of renal recovery. We further classified renal recovery into "complete renal recovery" (eGFR within 25% of the baseline eGFR), "incomplete renal recovery" (25% of more decline of reference eGFR) and "absent renal recovery" (permanent need for RRT for more than three months). Estimated GFR was based on known baseline serum creatinine levels. We reported a 90-day dialysis dependency rate of 9.0%. This was lower than the dialysis dependency rate reported in the FINNAKI trial (18.9% at 90 days) and higher than in the RENAL trial (5.6% at 90 days) [6, 40]. It needs to be mentioned that in both these studies, CRRT was the RRT modality of choice. As mentioned above, literature on the association of RRT modality with kidney outcome remains conflicting. A meta-analysis by Schneider et al suggested that CRRT as initial modality may be associated with better kidney outcome. However, this was mainly based on observational data which precluded to make firm conclusions [50].

In study III renal recovery was 56.7% at 90 days (56.7%), and 48.4% at 1-year. At the same one year time point, 32.6% of the patients had incomplete renal recovery and 19.0% had ESKD treated with RRT. Dialysis dependency increased over time to 28.1% at three years. Patients with ESKD more often had diabetes, CKD and oliguria at time of initiation of RRT. This is similar to findings in other cohort studies and meta-analyses [51-54]. Several studies demonstrated the long-lasting effects of an AKI(-RRT) episode on renal function. In a 10-year follow-up study of AKI survivors, Ponte et al found that over 50% of the patients failed to fully recover kidney function [55]. In addition, Gammelager et al found an increased five-year risk of developing ESKD after an AKI-RRT episode [56]. Finally, a large Swedish cohort study including more than 97,000 patients demonstrated that AKI is independently associated with increased risk of CKD and ESKD [57].

Our findings depict that one third of the patients of the study cohort had incomplete recovery at 1 year and is therefore actually at risk for developing ESKD. With only 34% of all AKI-RRT survivors seen by a nephrologist after hospital discharge, follow-up can be considered inadequate. Moreover, this proportion also includes patients with ESKD; hence, we can assume that the majority of patients with incomplete renal recovery lack adequate follow-up after their AKI-RRT episode. Although data concerning this topic are scarce, this patchy follow-up cannot be considered a local and therefore isolated problem. A sub-study of the RENAL trial demonstrated that the prevalence of proteinuria amongst survivors was almost 50%, stressing the increased long-term risk of death associated with AKI-RRT [44]. A more recent study in patients surviving ICU after an AKI-RRT episode reported a specialist nephrology follow-up in only 12% of the patients [58].

With regard to these data and taking into account the social and economic impact of chronic dialysis, specialized follow-up of survivors of severe AKI-RRT by a nephrologist may be justified. Follow-up strategies must focus on chronic proteinuria reduction strategies and the timely diagnosis of CKD [47].

2.3.3. MAKE In study III we reported the composite endpoint MAKE. Compared with single-outcome endpoints, this aggregate endpoint has a higher incidence than each of the component endpoints. As a consequence, it captures a greater proportion of patients with poor long-term outcomes [59].

However, in the present work, there was no association between MAKE and preexisting CKD, timing of RRT and modality of RRT. According to recent guidelines we reported the individual components of MAKE [60]. Consequently we found that MAKE was mainly determined by its biggest individual component, mortality. Ideally only components of similar clinical importance are combined [61]. The reported high mortality rates in study III may therefore have led to the predominance of the mortality component in MAKE impairing its interpretation.

2.4 OBJECTIVE 4 HEALTH RELATED QUALITY OF LIFE

Naturally, mortality and dialysis dependency are decisive endpoints. Recently, patient-reported outcomes such as HrQOL have gained interest as they gather information provided by the patient himself about his/her personal experience of the disease, treatment and care. HrQOL is a relevant clinical endpoint as it attempts to assess the burden of disease when surviving an AKI-RRT episode whether dialysis dependent or not. Remarkably, our research showed that long-term HrQOL had the same evolution over time in AKI-RRT and in non-AKI-RRT patients. A recent meta-analysis that also included our study confirmed these findings. It was concluded that critically ill patients with AKI-RRT had impaired QOL compared with the general population, but not different from that of ICU survivors without AKI. Of the 18 studies included in the meta-analysis, our study had the second longest follow-up period. When implementing the Modified Downs and Black Scores for Included Studies, which is a quality index, our study protocol scored 15 out of 19 points. Further, only 6 out of 18 studies reported pre-AKI baseline data and assessed HrQOL using standardized and validated PRO instruments (SF-36 and EQ-5D) at fixed durations of follow-up [62].

The need for RRT in severely ill patients significantly increases the burden of disease. It may be a pivotal moment in the decision-making whether or not to withdraw life-sustaining therapy. Our findings shed a new light on the discussion. Indeed, AKI-RRT in critically ill patients heavily impacts their long-term survival, but patients who survive ICU have a HrQOL comparable with critically ill patients without an AKI-RRT episode during their ICU stay. Even more surprisingly, the majority of the AKI-RRT patients are willing to undergo similar far-reaching treatment in the ICU again when necessary. However, some limitations have to be noticed. Firstly, studies tend to simplify the reality because of statistical purposes. Their presented evidence is population-based but is not able to make firm conclusions on the individual level. As a consequence medical treatment should not exclusively be based on the available evidence but should also be guided by ethical decision-making with respect for the wishes and values of the patient. Secondly, due to therapy restrictions, not all patients were referred to the ICU or were dialyzed during their ICU stage. When these patients survive critical illness, they may experience a decreased HrQOL after hospital discharge. This may adversely impact their willingness to undergo a new ICU admission with its inherent drawbacks. Of note, the ICU stay with its inherent high mortality rates in AKI-RRT patients likely reflects the concept of “survival of the fittest”. Once the ICU has been survived, former AKI-RRT patients tend to function as well as non-AKI RRT patients after hospital discharge. Finally, only patients who survived the ICU were interviewed. Patients who stayed in the ICU for a long time but eventually died could not be studied. This limitation may bias our results. However, it would be interesting to evaluate the burden of disease in these patients and their relatives.

REFERENCES

[1] Gibney et al. Timing of initiation and discontinuation of RRT in AKI: Unanswered key questions. CJASN 2008;3:876-80

[2] KDIGO AKI Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:1-138

[3] Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM: Quality of life after intensive care: a systematic review of the literature. Crit Care Med 2010, 38(12):2386-2400.

[4] Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E et al: Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005, 294(7):813-818.

[5] Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D et al: Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015, 41(8):1411-1423.

[6] Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, Haapio M, Inkinen O, Parviainen I, Suojaranta-Ylinen R et al: Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 2013, 39(3):420-428.

[7] Siew ED, Davenport A: The growth of acute kidney injury: a rising tide or just closer attention to detail? Kidney Int 2015, 87(1):46-61.

[8] Wald R, Bagshaw SM: The Timing of Renal Replacement Therapy Initiation in Acute Kidney Injury. Semin Nephrol 2016, 36(1):78-84.

[9] Teschan PE, Baxter CR, O'Brien TF, Freyhof JN, Hall WH: Prophylactic hemodialysis in the treatment of acute renal failure. Ann Intern Med 1960, 53:992-1016.

[10] Ostermann M, Dickie H, Barrett NA: Renal replacement therapy in critically ill patients with acute kidney injury--when to start. Nephrol Dial Transplant 2012, 27(6):2242-2248.

[11] Bagshaw SM, Wald R, Barton J, Burns KE, Friedrich JO, House AA, James MT, Levin A, Moist L, Pannu N et al: Clinical factors associated with initiation of renal replacement therapy in critically ill patients with acute kidney injury-a prospective multicenter observational study. J Crit Care 2012, 27(3):268-275.

[12] Waikar SS, Bonventre JV: Can we rely on blood urea nitrogen as a biomarker to determine when to initiate dialysis? Clin J Am Soc Nephrol 2006, 1(5):903-904.

[13] Bellomo R, Lipcsey M, Calzavacca P, Haase M, Haase-Fielitz A, Licari E, Tee A, Cole L, Cass A, Finfer S et al: Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis. Intensive Care Med 2013, 39(3):429-436.

[14] Levraut J, Ciebiera JP, Jambou P, Ichai C, Labib Y, Grimaud D: Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. Crit Care Med 1997, 25(1):58-62.

[15] Bellomo R: Bench-to-bedside review: lactate and the kidney. Crit Care 2002, 6(4):322-326.

[16] Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury.J Crit Care. 2009 Mar;24(1):129-40

[17] Wilson FP: A policy of preemption: the timing of renal replacement therapy in AKI. Clin J Am Soc Nephrol 2014, 9(9):1510-1512.

[18] Gettings LG, Reynolds HN, Scalea T: Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. Intensive Care Med 1999, 25(8):805-813.

[19] Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D et al: Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med 2016, 375(2):122-133.

[20] Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, Boanta A, Gerß J, Meersch M: Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA 2016, 315(20):2190-2199.

[21] Macedo E, Bouchard J, Soroko SH, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL, Study PICARD: Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. Crit Care 2010, 14(3):R82.

[22] Perko MJ, Jarnvig IL, Højgaard-Rasmussen N, Eliasen K, Arendrup H. Electric impedance for evaluation of body fluid balance in cardiac surgery patients. J Cardiothorac Vasc Anesth 2001;15:44-48.

[23] Prowle JR, Leitch A, Kirwan CJ, Forni LG. Positive fluid balance and AKI diagnosis: assessing the extent and duration of "creatinine dilution". Intensive Care Med 2015;41:160

[24] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Network AKI: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007, 11(2):R31.

[25] Yerram P, Karuparthi PR, Misra M: Fluid overload and acute kidney injury. Hemodial Int 2010, 14(4):348-354.

[26] Van Biesen W, Vanholder R, Lameire N: Defining acute renal failure: RIFLE and beyond. Clin J Am Soc Nephrol 2006, 1(6):1314-1319.

[27] Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, Laurila JJ, Mildh L, Reinikainen M, Lund V et al: Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012, 16(5):R197.

[28] Ostermann M, Chang RW: Correlation between parameters at initiation of renal replacement therapy and outcome in patients with acute kidney injury. Crit Care 2009, 13(6):R175.

[29] Demirkiliç U, Kuralay E, Yenicesu M, Cağlar K, Oz BS, Cingöz F, Günay C, Yildirim V, Ceylan S, Arslan M et al: Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg 2004, 19(1):17-20.

[30] Elahi MM, Lim MY, Joseph RN, Dhannapuneni RR, Spyt TJ: Early hemofiltration improves survival in post-cardiotomy patients with acute renal failure. Eur J Cardiothorac Surg 2004, 26(5):1027-1031.

[31] Sugahara S, Suzuki H: Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. Hemodial Int 2004, 8(4):320-325.

[32] Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL: Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. Am J Kidney Dis 2008, 52(2):272-284.

[33] Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, Bagshaw SM: A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care 2011, 15(1):R72.

[34] Wierstra BT, Kadri S, Alomar S, Burbano X, Barrisford GW, Kao RL: The impact of "early" versus "late" initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis. Crit Care 2016, 20(1):122.

[35] Xu Y, Gao J, Zheng X, Zhong B, Na Y, Wei J: Timing of initiation of renal replacement therapy for acute kidney injury: a systematic review and meta-analysis of randomized-controlled trials. Clin Exp Nephrol 2016.

[36] Vaara ST, Reinikainen M, Wald R, Bagshaw SM, Pettilä V, Group FS: Timing of RRT based on the presence of conventional indications. Clin J Am Soc Nephrol 2014, 9(9):1577-1585.

[37] Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, Paganini EP, Chertow GM, Disease PtICiAR: Spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney Int 2004, 66(4):1613-1621.

[38] Srisawat N, Sileanu FE, Murugan R, Bellomod R, Calzavacca P, Cartin-Ceba R, Cruz D, Finn J, Hoste EE, Kashani K et al: Variation in risk and mortality of acute kidney injury in critically ill patients: a multicenter study. Am J Nephrol 2015, 41(1):81-88.

[39] Ympa YP, Sakr Y, Reinhart K, Vincent JL: Has mortality from acute renal failure decreased? A systematic review of the literature. Am J Med 2005, 118(8):827-832.

[40] Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R et al: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009, 361(17):1627-1638.

[41] Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, Godinez-Luna T, Svenson LW, Rosenal T: Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 2005, 9(6):R700-709.

[42] Korkeila M, Ruokonen E, Takala J: Costs of care, long-term prognosis and quality of life in patients requiring renal replacement therapy during intensive care. Intensive Care Med 2000, 26(12):1824-1831.

[43] Ahlström A, Tallgren M, Peltonen S, Räsänen P, Pettilä V: Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Med 2005, 31(9):1222-1228.

[44] Gallagher M, Cass A, Bellomo R, Finfer S, Gattas D, Lee J, Lo S, McGuinness S, Myburgh J, Parke R et al: Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLoS Med 2014, 11(2):e1001601.

[45] Kellum JA, Bellomo R, Ronco C: Kidney attack. JAMA 2012, 307(21):2265-2266.

[46] Truche AS, Darmon M, Bailly S, Clec'h C, Dupuis C, Misset B, Azoulay E, Schwebel C, Bouadma L, Kallel H et al: Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: impact on mortality and renal recovery. Intensive Care Med 2016, 42(9):1408-1417.

[47] Chawla LS, Kimmel PL: Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int 2012, 82(5):516-524.

[48] Coca SG, Singanamala S, Parikh CR: Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012, 81(5):442-448.

[49] Rimes-Stigare C, Awad A, Mårtensson J, Martling CR, Bell M: Long-term outcome after acute renal replacement therapy: a narrative review. Acta Anaesthesiol Scand 2012, 56(2):138-146.

[50] Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, Cass A, Gallagher M: Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med 2013, 39(6):987-997.

[51] Rimes-Stigare C, Frumento P, Bottai M, Mårtensson J, Martling CR, Bell M: Long-term mortality and risk factors for development of end-stage renal disease in critically ill patients with and without chronic kidney disease. Crit Care 2015, 19:383.

[52] Sawhney S, Mitchell M, Marks A, Fluck N, Black C: Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. BMJ Open 2015, 5(1):e006497.

[53] Venot M, Weis L, Clec'h C, Darmon M, Allaouchiche B, Goldgran-Tolédano D, Garrouste-Orgeas M, Adrie C, Timsit JF, Azoulay E: Acute Kidney Injury in Severe Sepsis and Septic Shock in Patients with and without Diabetes Mellitus: A Multicenter Study. PLoS One 2015, 10(5):e0127411.

[54] Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordoñez JD, Go AS: Nonrecovery of kidney function and death after acute on chronic renal failure. Clin J Am Soc Nephrol 2009, 4(5):891-898.

[55] Ponte B, Felipe C, Muriel A, Tenorio MT, Liaño F: Long-term functional evolution after an acute kidney injury: a 10-year study. Nephrol Dial Transplant 2008, 23(12):3859-3866.

[56] Gammelager H, Christiansen CF, Johansen MB, Tønnesen E, Jespersen B, Sørensen HT: Five-year risk of end-stage renal disease among intensive care patients surviving dialysis-requiring acute kidney injury: a nationwide cohort study. Crit Care 2013, 17(4):R145.

[57] Rimes-Stigare C, Frumento P, Bottai M, Mårtensson J, Martling CR, Walther SM, Karlström G, Bell M: Evolution of chronic renal impairment and long-term mortality after de novo acute kidney injury in the critically ill; a Swedish multi-centre cohort study. Crit Care 2015, 19:221.

[58] Kirwan CJ, Blunden MJ, Dobbie H, James A, Nedungadi A, Prowle JR: Critically ill patients requiring acute renal replacement therapy are at an increased risk of long-term renal dysfunction, but rarely receive specialist nephrology follow-up. Nephron 2015, 129(3):164-170.

[59] Billings FT, Shaw AD: Clinical trial endpoints in acute kidney injury. Nephron Clin Pract 2014, 127(1-4):89-93.

[60] Freemantle N, Calvert M: Composite and surrogate outcomes in randomised controlled trials. BMJ 2007, 334(7597):756-757.

[61] Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC: Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ 2010, 341:c3920.

[62] Villeneuve PM, Clark EG, Sikora L, Sood MM, Bagshaw SM: Health-related quality-of-life among survivors of acute kidney injury in the intensive care unit: a systematic review. Intensive Care Med 2016, 42(2):137-146.

8

1. Limitations

2.1 LIMITATIONS DUE TO STUDY DESIGN AND INCLUSION CRITERIA

We acknowledge that this work has a number of shortcomings. First, due to the recruitment of patients from a single tertiary care center, our findings may lack external validity. However, the presented data are based on a large cohort of patients. Furthermore, our epidemiological data on incidence of AKI-RRT in critically ill patients as well as the reported mortality rates were similar to other findings in literature suggesting our study cohort may reflect a typical ICU population as seen in the Western world. Second, study I and II were retrospective studies on a limited number of patients and can therefore only be hypothesis generating. To correct for this observational design we used multivariate regression models and included a propensity score to adjust possible bias. In addition, the findings presented in study I were confirmed by a more recent study of Ostermann et al [1]. Third, the present work exclusively focuses on critically ill patients with AKI-RRT. Obviously, this is a very specific cohort of patients and results may therefore not be valid in other patient populations. Also, some patients may have qualified for RRT, but actually not have been treated with RRT e.g. if it was considered futile in their specific setting. Additionally, other groups may use other, more or less stringent criteria to initiate RRT.

2.2 HANDLING MISSING DATA

As in most epidemiological studies, we faced the unavoidable and common problem of lacking or "missing" data. A methodological survey of the top 5 general medical journals found that 87% of published trials reported missing data for the primary outcome [63]. Importantly, missing data may undermine the validity of research results. Therefore, dealing adequately with missing data is of great importance. It requires careful examination of the data which can be very challenging. The risk of bias due to missing data depends on the reasons why data are missing. Basically, there are two "patterns of missingness". Data can be "Missing At Random" (MAR) meaning that the underlying missing data mechanism is independent of the unobserved data and therefore "ignorable". Missing data may also be due to a "Missing Not At Random" (MNAR) mechanism, meaning that the missingness mechanism depends on unobserved data and therefore "non-ignorable" [2]. Several strategies were proposed to deal with missing data. First, a priori plans to minimize missing data are imperative. Second is to report the reasons for missingness and the pattern for missingness (at random or not). Third, one can opt to include only complete cases in the analysis. This approach seems logical, but only gives valid results if the probability of being a complete case is independent of outcome. Fourth, a widely used statistical method for ad hoc handling of MAR data is multiple imputation. The technique is based on the assumption that the missing data are ignorable. It allows individuals with missing data to be included in the analysis and has therefore the potential to improve the validity and power of the research findings. Unfortunately it is not possible to distinguish between MAR and MNAR using observational data. So finally, a sensitivity analysis may be necessary

to address the problem of missing data. Basically a sensitivity analysis gives an idea of what would happen if the data are MNAR by investigating possible violations of the MAR assumption. It assesses the robustness of the main findings under different assumptions regarding the outcomes of participants with missing data [3,4]. For example, when there are missing outcome data, a common sensitivity analysis is to explore "best" and "worst" case scenarios by replacing missing values with good outcomes in one group and bad outcomes in the other group. If the results are reasonably consistent, one can assume that even if data are MNAR, they would not compromise the findings. However, the MNAR hypothesis is rarely explored, although it has been recommended by various guidelines.

We used the above mentioned guidelines to handle the missing data in the present work. The retrospective design of Study I and Study II made a priori planning to minimize missing data impossible. Study III and IV had a prospective design, so a strategy to minimize missing data was set-up more easily. Patients were prospectively included, which allowed more complete medical files and baseline data. In addition, follow-up was strict. When necessary, the general practitioner (GP) was contacted to complete the data. When unavoidable, we reported the missing cases by presenting a flow chart in all studies and clarified the reasons for missing data. Most missing cases were MAR as they were due to the gradual introduction of the PDMS. In all studies included in this thesis, we only analyzed cases when included in the PDMS. However, when confronted with additional missing data (mostly laboratory data) in these patients, we used a sensitivity analysis as an ad hoc approach to test the MNAR hypothesis. This was the case in Study I, II and III. No differences in outcome could be demonstrated, suggesting that missing data were MAR and could therefore only have led to limited bias.

2. Future perspectives

Our findings and also those of others highlighted the urgent need for better evidence to guide us on the optimal timing of RRT for AKI. As indicated in the discussion above, 3 prospective studies have addressed early initiation of RRT based on KDIGO criteria [5-7]. In addition, to these studies, 2 other large studies are currently being conducted. The Initiation of Dialysis Early Versus de-Layed in Intensive Care Unit (IDEAL-ICU) study is a French multicenter RCT to assess whether the timing of initiation of RRT has an impact on 90-day mortality in critically ill patients with AKI during the initial phase of septic shock (clinicaltrials.gov NCT01682590). In addition the Canadian Standard versus Accelerated Initiation of RRT in Acute Kidney Injury (STARRT-AKI) trial is a prospective multicenter RCT investigating the impact of timing of initiation of RRT on patient and kidney outcome (clinicaltrials.gov NCT02568722). Together these studies will include more than 3,500 patients, and will therefore have sufficient power to address this issue. However, it is uncertain whether a certain AKI stage cut-off will be the optimal tool to indicate optimal timing of RRT. This may already be illustrated by the diverging signals generated by the AKIKI, STARRT-AKI, and ELAIN studies [5-7]. There is an ongoing need for an adequately powered trial that is applicable to current practice.

The present work focused on long-term patient and kidney outcomes in ICU patients with AKI-RRT. We highlighted the impact of such an AKI-RRT episode during ICU stay on outcome measures such as mortality, renal recovery, and evolution towards ESKD. As many as one-third of the patients in our cohort had incomplete kidney recovery. Somewhat surprisingly only 34% of the patients had follow-up of the kidney function by a nephrologist. This follow-up is not protocol driven but based on clinical and renal status of the patient at discharge of the ICU and/or hospital. However, follow-up of patients in the RENAL study revealed that a large proportion of AKI-RRT survivors

had albuminuria and decreased eGFR [8]. Following these findings, we think that a prospective long-term outcome study on the potential benefit of nephrological follow-up after an AKI-RRT episode in critically ill patients seems to be imperative. Ideally such a study includes all adult critically ill patients with AKI-RRT, discharged from ICU. However, one could also consider including patients who had less severe AKI. Possible endpoints are the incidence of CKD and evolution to ESKD. Possible outcome measures are mortality, renal recovery, dialysis dependency. Follow-up during hospital stay may be provided by the nephrologist. However, after hospital discharge, the patient may be followed by the GP in alternation with the nephrologist at defined time intervals, or by the GP with telephonic, e-based or other back-up by the nephrologist. Another option is the creation of specialized post-AKI clinics [9]. It is important to report every AKI episode in the medical history of the patient. Follow-up should focus on monitoring kidney function (assessing evolution of sCR concentration and GFR over time, screening for (micro)albuminuria) and the detection and treatment of risk factors for the development of CKD. Known risk factors are arterial hypertension, diabetes, cardiac failure and vascular disease. In addition, nephrotoxic drugs (e.g. NSAIDS) and intravascular contrast media should be avoided [10]. The GP should be provided criteria for referral of patients with deteriorating CKD to the nephrologist. Obviously, this follow up should be continued in patients who developed CKD. At present, we lack data on how long this follow up should be continued in patients with complete recovery of kidney function.

In the present work the composite endpoint MAKE falls short of expectations. As MAKE was mainly determined by its biggest component mortality, this aggregate endpoint didn't add much value compared with the classical mortality endpoint. However composite endpoints remain of interest as they may reduce sample size and may increase statistical efficiency [11]. Ideally, future research entails the weighing up of the individual components of MAKE to minimalize distortions by these individual endpoints. Only then can the correct interpretation of MAKE be made.

In addition, another opportunity lies in the introduction of advanced statistical techniques in the field of AKI. A randomized clinical trial is the standard design to quantify the causal effect of an intervention. However, in many cases we have to rely on observational data. In order to estimate this effect from observational data it is necessary to adjust not only for baseline covariates but also for time-varying confounders such as indicators of disease progression. Marginal structural models provide a way to overcome the drawbacks of standard models by estimating causal effects [12]. To this date this approach seems to be lacking in the field of AKI. However, standard definitions for AKI have only been established very recently. It is to be expected that these statistical techniques will find their way into the field of AKI which is characterized by the complex dynamics and interplay between severity of illness, the development of AKI eventually leading to the administration of RRT and outcome. Future understanding of this epidemiology will play a vital role in diminishing the public health burden of AKI. Fortunately, the clinical study of AKI has been facilitated in recent years by the increasing availability of administrative data [13]. According to Bagshaw et al, AKI may be an ideal syndrome to focus on. AKI is common in hospitalized patients and it is associated with an increased risk for adverse outcomes. Further, patients suffering from AKI consume great resources and have a significant longer ICU and hospital stay. Finally, recent data have stressed the suboptimal care of patients with AKI [14]. Recently, the ADQI convened a panel of experts to examine how big data can enhance scientific progress and improve outcomes in AKI. They raised some concerns over the quality of the data. Data obtained from large, national administrative datasets are usually not collected for conducting clinical research. Further the current coding structure of administrative data is hampered by a lack of sensitivity. The reduced awareness for AKI and the risk for subjective coding limits the understanding of AKI. However,

these limitations emphasized opportunities to improve the quality of the data [15]. In conclusion, the use of big data in healthcare holds great promise to drive innovation, address knowledge gaps in AKI and improve outcomes for patients suffering from AKI.

Finally, we assessed the long-term HrQOL in patients after an AKI-RRT episode. Some of the interviewed patients and peers remembered their ICU stay as harsh and disturbing. Others highlighted the lack of autonomy and self-determination. These experiences can be an incentive to evaluate and optimize the "humanization" of the ICU.

Several problems and mechanisms can contribute to dehumanization of the ICU [16]. The admission of a critically ill patient on the ICU is frequently associated with unrealistic expectations of that patient, his/her family members or the referring physician. Technological advances have enabled clinicians to prolong lives of critically ill patients even when there is no hope for successful treatment of the underlying disease. On the contrary, most people believe that futile treatments should not be provided. However, differences in people's perceptions of futile treatment, the burden of disease, severity of illness and the "grade of invasiveness" of medical interventions may alter the ICU in a hostile and brutal place for all involved.

Furthermore, the individual's sense of self, cornerstone of contemporary Western bioethics, is under threat [17]. The focus on self-determination can be difficult to apply in the ICU because the patient may lack the intact consciousness required to exercise that autonomy. The presence of altered consciousness, severity of illness and the unavoidable uncertainty about life and death may induce a kind of inertia and even "compassion fatigue" in ICU caregivers working in a demanding setting [18]. To cope with this uncertainty relatives and caregivers see patients as belonging in the group of non-survivors or survivors. In non-survivors, palliative care should be optimized. On the contrary, in the survivor group, technological imperatives focused on prolonging life predominate. Unfortunately it is very difficult to categorize the critically ill patient. The known prognostic scores that adjust for severity of illness are useful tools for hospital benchmarking. However, they can't predict individual outcome [19]. As the current prognostication is not accurate enough to eliminate uncertainty, this further increases the risk for "dehumanization" of the ICU.

Several measures can be taken to humanize the ICU and improve respect for the patient and his/her family. Focusing on the wishes and values of the individual is the cornerstone of patient-centered care. Advanced care planning, a well-known concept in the geriatric literature should be introduced in the ICU. It is a process by which patients, together with their physicians and family establish goals and preferences for future care. Implementation of ACP improves the quality of dying [20]. Ideally, ACP is organized previous to an ICU admission to avoid unintended admissions. ACP may increase the awareness that optimal care may encompass withdrawing life-sustaining therapy as a respectful and valuable alternative for life-prolonging interventions in terminally-ill patients. Further, engagement of the patient, his/her family and the ICU team may ease the burden of critical illness by decreasing the sense of isolation and helplessness [21]. In addition, open visitation policies are crucial. They strengthen the social networks of the patient and allow families to contribute to his/her recovery [22]. Finally, giving honest information regarding diagnosis and prognosis is the starting point for an optimal communication. Information tailored to the patient and his/her family improves general satisfaction and decreases stress among families of critically ill patients near death [23].

Respect and dignity are often used to describe the opposite of dehumanization. Some simple measures may improve respect for the patient: knowing his/her name, knocking on the door before entering the room, asking permission before examining the patient. As a consequence these values can be used as outcome measures to assess future quality of care and humanization of the ICU [24].

REFERENCES

[1] Ostermann M, Dickie H, Barrett NA: Renal replacement therapy in critically ill patients with acute kidney injury--when to start. Nephrol Dial Transplant 2012, 27(6):2242-2248.

[2] Héraud-Bousquet V, Larsen C, Carpenter J, Desenclos JC, Le Strat Y: Practical considerations for sensitivity analysis after multiple imputation applied to epidemiological studies with incomplete data. BMC Med Res Methodol 2012, 12:73.

[3] Akl EA, Briel M, You JJ, Sun X, Johnston BC, Busse JW, Mulla S, Lamontagne F, Bassler D, Vera C et al: Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. BMJ 2012, 344:e2809.

[4] Resseguier N, Giorgi R, Paoletti X: Sensitivity analysis when data are missing not-at-random. Epidemiology 2011, 22(2):282.

[5] Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A, Thorpe K, McIntyre L, Lamontagne F, Soth M et al: Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney Int 2015, 88(4):897-904.

[6] Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D et al: Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med 2016, 375(2):122-133.

[7] Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, Boanta A, Gerß J, Meersch M: Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA 2016, 315(20):2190-2199.

[8] Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R et al: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009, 361(17):1627-1638.

[9] Silver SA, Harel Z, Harvey A, Adhikari NK, Slack A, Acedillo R, Jain AK, Richardson RM, Chan CT, Chertow GM et al: Improving Care after Acute Kidney Injury: A Prospective Time Series Study. Nephron 2015, 131(1):43-50.

[10] KDIGO AKI Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:1-138Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011;79:1361-1369

[11] Freemantle N, Calvert M: Composite and surrogate outcomes in randomized controlled trials. BMJ 2007, 334(7597):756-757.

[12] Robins JM, Hernan MA, Brumback BA. Marginal structural models and causal interference in epidemiology. Epidemiology 2000, 11:550-560

[13] Nadkarni GN, Coca SG. Temporal trends in AKI: insights from big data.

[14] Bagshaw SM, Goldstein LG, Ronco R, Kellum JA. Acute kidney injury in the era of big data: the 15th Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). Editorial. Can J Kidney Health Disease 2016, 3:5

[15] Siew ED, Basu RK, Wunsch H, Shaw AD, Goldstein SL, Ronco C, Kellum JA, Bagshaw SM. Optimizing administrative datasets to examine acute kidney injury in the era of big data: workgroup statement from the 15th ADQI Consensus Conference.

[16] Brown SM. Through the valley of shadows: living wills, intensive care, and making medicine human. Oxford University Press, New York, 2016

[17] Taylor C. A secular age. Harvard University Press, Cambridge, 2007

[18] Embriaco N, Papazian L, Kentish-Barnes, Pochard F, Azoulay E. Burnout syndrome among critical care healthcare workers. Curr Opin Crit Care 2007, 13:482-488

[19] Zier LS, Sottile, Hong SY, Weissfield LA, White DB. Surrogate decision makers' interpretation of prognostic information: a mixed-methods study. Ann Intern Med 2012, 156:360-366

[20] Piers RD, van Eechoud IJ, Van Camp S, Grypdonck M, Deveugele M, Verbeke NC, Van Den Noortgate NJ. Advanced care planning in terminally ill and frail older persons. Patient Education Counseling 2013, 90:323-329

[21] Brown SM, Rozenblum R, Aboumatar H et al. Defining patient and family engagement in the intensive care unit. Am J Respir Crit Care Med 2015, 191:358-360

[22] Brown SM. We still lack patient centered visitation in intensive care units. BMJ 2015, 350h792

[23] Lautrette A, Darmon M, Megarbane B et al. A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med 2007, 356:469-478

[24] Sokol-Hessner L, Folcarelli PH, Sands KE. Emotional harm from disrespect: the neglected preventable harm. BMJ Qual Saf 2007, 24:550-553

Summary
Samenvatting

9

AKI is a frequent finding in ICU patients. Despite decades of progress in critical care it is associated with adverse outcomes such as increased LOS, short and long-term mortality and ESKD. In its most severe form AKI is treated with RRT. AKI-RRT in critically ill patients is associated with mortality, development of CKD and ESKD. The overall aim of this doctoral thesis was to describe the epidemiology of AKI in critically ill patients treated with RRT. Special attention was paid to some of the conventional indications of initiation of RRT. In addition, the short- and long-term patient and kidney outcomes and long-term quality of life in critically ill patients AKI-RRT were explored.

There is a longstanding consensus to initiate RRT in life-threatening situations such as severe acidosis, electrolyte disorders, the presence of uremic signs or in case of volume overload. However, the precise timing of initiation of RRT remains a matter of debate. The present work evaluated some conventional indications for initiation of RRT. First we investigated whether the commonly used serum urea cut-off concentrations for initiation of RRT had a possible predictive value for mortality. We found that they had no predictive value for hospital mortality in severely ill patients with AKI. Second, we explored another indication for initiation of RRT in critically ill patients with AKI: severe lactic acidosis. As literature describing this condition is scarce we described the epidemiology of SLA and determined possible factors influencing outcome. We found that severe lactic acidosis was present in about one third of critically ill patients with AKI treated with RRT. We demonstrated that the administration of RRT improved acid-base balance in most patients. Further, lactate concentration at initiation of RRT could not be used to discriminate between survivors and non-survivors. As a consequence, the administration of RRT may act as a bridge that treats the underlying cause of the acidosis.

We found that AKI-RRT occurred in 5.5% of patients admitted to the ICU. Mortality rates were high, with almost 60% of the patients dying during their hospital stay and approximately an additional 10% per year of the hospital survivors in the years following discharge. Mortality was associated with advancing age and clinical status at initiation of RRT. Further, renal recovery was limited. Almost one-fifth of the AKI-RRT survivors had ESKD at one year. Renal recovery was often incomplete and associated with comorbidities such as diabetes and CKD. These findings highlight the need for long-term nephrological follow-up.

Finally we described the long-term quality of life in this specific cohort of patients. These patients are amongst the most severely ill patients in the ICU. In addition, AKI-RRT patients who survive may develop CKD, including ESKD. As expected, their HrQOL was lower than the general population. However, despite the heavy burden of disease, their QOL was comparable to matched survivors without AKI-RRT. Moreover, the majority of the patients wanted to be readmitted to the ICU when needed.

Acuut nierfalen komt frequent voor op intensieve zorgen. Ondanks vooruitgang in de zorg voor de kritiek zieke patiënt blijft acuut nierfalen geassocieerd met een verlengd ziekenhuisverblijf, een hoge sterfte en evolutie naar terminaal nierfalen. In geval van zeer ernstig nierfalen wordt er nierfunctievervangende therapie of dialyse opgestart. Patiënten met ernstig acuut nierfalen behandeld met dialyse hebben een verhoogd risico op sterfte en de ontwikkeling van chronisch en terminaal nierfalen. Het doel van dit doctoraatswerk is de epidemiologie van deze specifieke cohorte van patiënten te beschrijven. Speciale aandacht wordt besteed aan de optimale timing van start van dialyse. Verder worden de korte- en langetermijn effecten van acuut nierfalen behandeld met dialyse op overleving, nierfunctie en kwaliteit van leven uitgebreid behandeld.
Er is een algemene consensus rond het opstarten van nierfunctievervangende therapie in geval van levensbedreigende situaties zoals ernstige acidose, elektrolietenstoornissen, de aanwezigheid van uremische complicaties of in geval van ernstige tekenen van overvulling. Nochtans is er geen consensus omtrent de exacte timing waarop dialyse dient opgestart te worden. Dit proefschrift bespreekt een aantal klassieke indicaties tot opstarten van dialyse. Vooreerst werden de klassieke serum ureum cut-off concentraties waarop vervolgens dialyse wordt gestart uitvoerig bestudeerd. We konden besluiten dat er geen verband was tussen deze serum ureum waarden bij de start door dialyse en ziekenhuissterfte. Vervolgens werd de conditie van ernstige lactaatacidose grondig bestudeerd. Hoewel ernstige lactaatacidose een indicatie voor het opstarten van dialyse is, vindt men weinig literatuur die deze conditie behandeld. We beschreven uitvoerig de epidemiologie van ernstige lactaatacidose en poogden determinanten van sterfte te bepalen. We stelden vast dat ernstige lactaatacidose tot in 1/3 van de kritiek zieke patiënten met ernstig nierfalen behandeld met dialyse voorkomt. Ernstige lactaatacidose geeft aanleiding tot een hoge sterfte op intensieve zorgen maar de absolute van het serum lactaat bij start dialyse is geen hulp bij het onderscheiden van patiënten die al dan niet zouden overleven. Nierfunctievervangende therapie zorgde wel bij deze patiënten voor een verbeterde zuurbase balans. Aldus kan dialyse in deze patiënten een tijdskader creëren waarbinnen de onderliggende oorzaak van de lactaatacidose kan behandeld worden.
Dit doctoraatswerk toonde aan dat 5.5% van de patiënten opgenomen op de afdeling intensieve zorgen lijdt aan acuut nierfalen behandeld met nierfunctievervangende therapie. De ziekenhuissterfte in deze groep van patiënten loopt op tot 60%. Na ontslag uit het ziekenhuis noteerden we bij de overlevenden aan bijkomende sterfte van 10% per jaar in de jaren volgend aan het ziekenhuis ontslag. Er was een duidelijk verband aantoonbaar tussen sterfte en leeftijd en de klinische toestand op het ogenblik van start van dialyse. Bovendien was het herstel van de nierfunctie eerder beperkt. We evalueerden de nierfunctie een jaar na ontslag uit het ziekenhuis en rapporteerden een terminaal nierfalen in 1/5 van de patiënten. Een onvolledig herstel van nierfunctie werd frequent gezien wanneer de patiënten gekend waren met diabetes en chronisch nierfalen. Deze bevindingen bevestigen de noodzaak voor een gedegen follow-up van de nierfunctie in deze specifieke groep van patiënten.
Als laatste werd de kwaliteit van leven na ontslag uit het ziekenhuis uitvoerig bestudeerd. Zoals verwacht was de levenskwaliteit lager dan van een verglijkbare populatie die niet werd opgenomen op intensieve zorgen. Verrassend genoeg was de kwaliteit van leven bij patiënten na nierfalen behandeld met dialyse vergelijkbaar met kritiek zieke patiënten zonder nierfalen behandeld met dialyse. Bovendien waren ze bereid dezelfde intensieve behandeling opnieuw te ondergaan indien nodig.

Dankwoord

Met het schrijven van dit dankwoord leg ik de laatste hand aan mijn doctoraatswerk. Tijdens deze zeer intense periode in mijn leven maakte ik niet alleen als wetenschapper maar ook als mens een groeiproces door. Het afronden van deze thesis, een “landmark” in mijn leven, is dan ook het ideale moment om stil te staan bij de dingen die er echt toe doen, te bedanken en vooruit te kijken naar nieuwe kansen en opportuniteiten. Het combineren van dit doctoraatswerk met een full-time job als clinicus en als vader en echtgenoot in een uitbreidend gezin was verre van evident en slechts mogelijk dankzij de hulp van velen.

Eric, bedankt voor alles! Jij maakte het voor mij mogelijk om als externe arts deze thesis te schrijven. Je legde de lat hoog en pushte mij vaak tot de limieten van mijn kunnen, maar je bleef steeds in mij geloven. Je deur stond steeds open voor advies. Je introduceerde me in de “kidney section” van de Europese vereniging voor intensieve zorgen (ESICM) waar ik vele interessante mensen ontmoette. Daarnaast liet je me ook kennis maken met de Italiaanse kunst van het leven in Vicenza. Bovenal apprecieer ik de vele informele en vriendschappelijke gesprekken met jou.

Professor Vanholder, hartelijk dank voor uw input zowel op academisch maar ook op grammaticaal vlak. Ik stond telkens versteld van uw snelle reactie en het was bijgevolg elke keer opnieuw uitkijken naar uw kritische maar steeds opbouwende feedback.

Professor Decruyenaere, bedankt voor het faciliteren van dit project, de toegang tot de elektronische databases en het nalezen van elke publicatie. Chris en Veerle, bedankt voor het uitvoeren van de soms ingewikkelde queries op de databases. Stefaan, Sofie, Veerle en Joke, eveneens bedankt voor het ingeven, opzoeken en aanleveren van data. Eveneens bedankt aan de study nurses Patrick, Patsy, Jo en Daniella
Ik houd er aan ook Professor Dhondt en Professor De Waele als leden van de begeleidingscommissie te bedanken voor het nalezen van alle manuscripten. Eveneens een merci aan Professor Annemans en Professor Benoit voor het nalezen van de paper omtrent kwaliteit van leven. Dominique, hopelijk volgen er in de toekomst nog vele aangename filosofische en existentiële discussies bij een goed glas wijn!

Eveneens een bedankje aan collega-doctorandus Sandra. Ons beider werk smeekte om een samenwerking. Al was het soms dansen op een slappe koord, toch ben ik blij met het mooie resultaat van deze synergie. Zo veranderden de vele telefonische enquêtes patiënten van anonieme “opnamenummers” in mensen met vaak veelzeggende stemmen. Ik wens je oprecht veel succes bij het afronden van jouw doctoraatswerk.

De collega’s anesthesie uit az groeninge wens ik eveneens te bedanken voor hun flexibiliteit wanneer ik weer eens naar Gent moest om het een en ander uit te klaren. De groeikansen die ik er elke dag krijg apprecieer ik enorm.

Fran, jij introduceerde me in de wondere wereld van de grafische vormgeving! Je gaf dit manuscript haar professionele lay-out mee en verpakte het in een prachtig jasje, precies zoals ik het gewenst had.

Het schrijven van deze thesis had ook een grote invloed op mijn gezinsleven. Dankzij Eva werden mijn “schrijf- en onderzoeksmomenten” jarenlang gebufferd. Ondanks haar drukke job maakt zij elke dag van ons huis een warme thuis voor het gezin met onze drie fantastische kinderen Louise-Marie, Emile en Hélène.

Een speciaal woordje van dank aan mijn mama. Zonder haar onuitputtelijke steun, zowel moreel en financieel, was mijn opleiding geneeskunde, anesthesie, intensieve zorgen en bijgevolg dit doctoraatswerk niet mogelijk. Geen inspanning was haar teveel. Een welgemeende merci voor alles! Zelf papa zijnde apprecieer ik des te meer het vaderlijk advies dat ondanks alle kennis en wetenschap de bedside klinische blik nooit uit het oog mag verloren worden. Wijze woorden van een succesvol huisarts op rust.

Verder wens ik nog mijn familie en vrienden te bedanken. Jeroen en Steve, bedankt voor jullie interesse en de mogelijkheid tot het afdrukken van de thesis volgens het “very-just-in-time” principe! Tante en nonkel Mark, jullie rotsvast vertrouwen in het afwerken van deze thesis was een grote steun voor mij. Annie, Dirk, Ruben, Sanne en Francine, bedankt voor jullie luisterend oor, ook wanneer het eens minder vlot ging. Ook aan de rest van de familie, bedankt voor jullie aanmoedigingen. Stijn en Christophe, vrienden van het eerste uur, ook jullie wens ik te bedanken voor de welgemeende interesse in dit project. Eveneens een welgemeende merci voor het supporteren door de vrienden die ik aan de schoolpoort in Kruishoutem heb leren kennen!

Ik wil dit dankwoord afsluiten met een anekdote. Toen ik als arts in opleiding mijn stage nefrologie afsloot, vertelde ik Professor Lameire dat ik me wenste te specialiseren in de anesthesie eerder dan de nefrologie. Hij wenste me veel succes maar kon niet nalaten te vermelden dat ik op de een of andere manier terug bij nefrologie zou terechtkomen. Zijn woorden waren in zekere zin profetisch en maken nu de cirkel rond.

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EPIDEMIOLOGY AND OUTCOME IN INTENSIVE CARE PATIENTS WITH ACUTE KIDNEY INJURY TREATED WITH RENAL REPLACEMENT THERAPY

Editor, doctorandus
Wouter De Corte

Design & artwork
Fran Van de Velde
wearesuperset.be

Printing
Stevens Print
Merelbeke, België

Format
180mm x 270mm

Grid
12pt baseline grid

Typeset in
Work Sans Thin
Work Sans Extralight
Work Sans Light
Work Sans Regular
Work Sans Medium

Paper
Opakal 60gsm
Pop'set Poppy 320gsm
Lessebo Design
White 1.3 100gsm
Clairefontaine Pearl 120gsm

Extent
152 pages

Inks
Pantone 1795U
Pantone Cool Gray 1U

Binding
Sewn